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MONOCYTIC LEUKEMIA[1]

CHARLES W. WAINWRIGHT, M.D., AND G. LYMAN DUFF, M.D.

From the Department of Medicine and the Department of Pathology of the Johns Hopkins University School of Medicine

Submitted for publication January 27, 1936

That myeloid and lymphoid leukemia are two separate forms of disease has been firmly established for more than a quarter of a century. In 1900 Naegeli's careful studies differentiated the myeloblast from the early lymphoid cell, and subsequent observations proved conclusively that leukemia with an acute course occurred in both the myeloid and lymphoid forms. In 1913 Reschad and Schilling described monocytic leukemia as a third type of acute leukemia, and the question of the origin of the monocyte was investigated with renewed interest. Since then diverse views on this subject have been advanced and stoutly defended. Clough recently has reviewed the evidence upon which these conflicting views rest and concludes that "the weight of evidence indicates that anatomically and physiologically monocytes have distinctive characteristics which separate them sharply from both granulocytes and lymphocytes—they have an independent source of origin and like the histiocytes can be traced to relatively primitive cells of the reticulo-endothelial system." He adds: "If their independent source of origin be accepted, theoretically the possible occurrence of monocytic leukemia as a pathological entity must be admitted."

During the past twenty years many cases of monocytic leukemia have been reported and the condition is now generally accepted by students of the blood as an independent disease. It is the opinion of Clough that many of the reported cases fulfill the requirements of the diagnosis. Forkner even attempts to differentiate the acute forms of leukemia upon clinical data alone and feels that the symptoms of acute monocytic leukemia are sufficiently distinctive to allow us

[1] Read before the American Clinical and Climatological Association at Princeton, New Jersey, on October 23, 1935.

to make the diagnosis even without the aid of the blood picture. On the other hand, Dameshek contends that the symptoms of acute monocytic leukemia differ so slightly from those of the other forms of acute leukemia that a histological examination of the blood is necessary in order to distinguish between them. Clough has pointed out that to justify the diagnosis of monocytic leukemia the disease should be characterized by a relative or absolute increase of the monocytes in the blood, by the presence of immature forms in the circulation and by pathological hyperplasia of the cells of the reticulo-endothelial system. Naegeli has consistently maintained that monocytic leukemia does not occur, contending that the cell in question is of myeloid origin. In all of the reported cases the monocytes of the blood have been relatively or absolutely increased, but in several generally accepted as instances of monocytic leukemia there have been early myeloid forms in the circulation and in some a late outpouring of granulocytic cells. Recently Gittins and Hawksley have reviewed the subject and divide the reported cases into four histological groups; (1) Leukemic monocytosis with generalized reticulo-endothelial hyperplasia; (2) leukemic monocytosis with a general infiltration with cells of similar appearance; (3) a combination of groups 1 and 2; (4) monocytosis with the histological features of myelosis. The attempt at classification makes it evident that there is considerable variation in what is called monocytic leukemia and that we are unable to apply the rigid differentiation customary in the well established forms of leukemia. It is for the purpose of pointing out these variations and the seeming transition which exists in this type of leukemia that we cite the following case.

A white housewife, of 40 years, was admitted to the Johns Hopkins Hospital December 4, 1934, complaining of severe headache, pain in the epigastrium and sore mouth. She had noticed ten days before admission that she was feeling vaguely ill but was unable to describe her symptoms precisely. The most noticeable one had been nervousness, at times so troublesome that she could not do her household work. Five days before admission she had awakened in the morning aching all over, particularly in the lower back. At this time she was examined but no physical abnormality could be detected except that the left tonsil was definitely enlarged and the temperature was 100°F. None of the superficial lymph nodes were enlarged. The following day the general aching and epigastric pain were worse and a day later the symptoms were still more aggravated and the left tonsil

was more enlarged. The throat was not sore but she complained of soreness under a dental plate, although there nothing objective was found. The temperature continued elevated and abdominal distention was added to the epigastric pain. She was admitted to the hospital five days after the definite onset of the illness and about two weeks after she had first noticed symptoms.

Her past and family history contributed nothing except that one year before this illness her physical condition had been reviewed. No important abnormalities had been found at that time. The tonsils were described as "cleanly removed." She had had a tonsillectomy a few years before. The blood picture was as follows. Hb. 85%; R.B.C. 4,300,000; W.B.C. 6,400. The differential count showed 58% P.M.N.; 34% Lymphocytes and 8% Monocytes.

On admission to the hospital the temperature was 100.2°, the pulse 120, respirations 22 and blood pressure 100/60. The patient was well developed and nourished but obviously acutely ill. The eyes were normal externally and the fundi showed no hemorrhages or exudates. The remaining teeth were in good condition but the gums were somewhat swollen, tender and spongy, particularly about the tooth margins. There was no bleeding from the gums. The tongue was coated but otherwise normal. The left tonsil was much enlarged and covered with a firmly adherent grayish white exudate. The right tonsil was also enlarged but not nearly so much as the left; it was somewhat inflamed but no exudate was present. The posterior pharyngeal wall was inflamed and the tufts of lymphoid tissue were prominent but there was no exudate or necrosis. The cervical lymph nodes in both anterior triangles were moderately enlarged and occasional small nodes were felt in the posterior cervical chains. The lungs were entirely clear and the heart showed nothing abnormal. A fine papillary rash was present over the abdomen and anterior thorax. There was moderate abdominal distention, and some tenderness on palpation in the mid-epigastrium was elicited. The liver seemed somewhat enlarged though the edge could not be definitely felt. The spleen was not palpable. The extremities showed nothing abnormal and the neurological examination was negative. No other lymph glands were palpable and no hemorrhagic manifestations in the skin or mucous membranes were found.

The examination of the blood showed definite anemia. Hb 70% with R.B.C. 2,820,000. The red cells were normal in appearance and the platelets were considered normal. The W.B.C. were 20,150, of which 2% were P.M.N., and 12% lymphocytes. The remaining 86% had many of the characteristics of monocytes, but there were large numbers of immature cells in the smears. The Wassermann reaction on the blood serum was negative, a chemical analysis of the blood gave normal results and the Van den Bergh reaction was negative. The voided urine contained a trace of albumin and occasional leucocytes were seen in the sediment. Blood cultures were negative and cultures from the tonsils yielded a mixed flora. Smears from the gums showed numerous bacteria, but no spirochetes or fusiform bacilli were seen.

The following day more intensive examinations of the blood showed that the clotting and bleeding time were normal and the platelet count was 209,000. The

peroxidase reaction of the cells thought to be monocytes was negative and with supra-vital stains these cells had the characteristics of monocytes. Some of the monocytes were very large, occasional ones had serrated borders and one had engulfed a blood platelet and another a red blood cell. Fresh blood samples mixed with a saline suspension of India ink showed that in a great proportion of the white cells the India ink particles were congregated in rosette fashion in the hof of the nucleus. In a few cells the ink particles were distributed in a ring about the nucleus. Occasional mononuclear cells with nucleoli contained a few particles of ink. All of these cells were held to be monocytes and the few definite polymorphonuclear neutrophiles seen contained few or no ink particles. The proportion of cells considered mature monocytes varied from 36% to 52%, whereas cells classified as premonocytes varied from 30% to 52% during the course of the illness. Frequently pseudopods were present and many of the cells contained digestion vacuoles. The nuclei were large, usually oval in outline, though many showed indentations. In many cells what appeared to be actual foldings of the nucleus were seen. The nuclei stained a light reddish purple with Wright's stain and showed a fine lacy network of the chromatin material. The cytoplasm of these cells was relatively abundant; it stained a pale bluish gray-green and contained reddish purple granules, giving it a dusty appearance. The granules appeared more plentiful, but not necessarily larger in the more mature cells. The cells were quite fragile and smudges were difficult to avoid. All transitions from the mature monocyte to blast cells were seen. The latter varied from 4% to 16% and their nuclei contained a thin lace-like network of the chromatin material. Nucleoli were present in many cells of this type. The cytoplasm of these cells was more basophilic than that of the more mature cells but much less so than that of typical myeloblasts. A few granules were seen in the cytoplasm but they were frequently absent and seemed to be in direct proportion to the maturity of the cell. No cells were seen which were considered transitions from these blast cells to more mature cells of the granular series. Very few myelocytes were seen but these became slightly more abundant as the disease advanced and as the anemia became more pronounced. Several cells were seen in mitotic division. Many of the abnormal cells were larger than the average and showed the characteristics of histiocytes but were not classified separately.

Course in the hospital: The patient's general condition became steadily worse, the temperature rose to 103° and 104° and remained at this level. The gums continued to swell until they extended to the edges of the teeth and gradually became necrotic. Numerous hemorrhagic blebs developed at the margins of the areas of necrosis away from the teeth. The entire mouth was very sore, the tonsils met in the midline and became extensively necrotic. Necrotic areas with hemorrhagic blebs at their margins appeared on the hard palate. The glands of the neck, particularly under the rami of the jaw, continued to enlarge, attaining the size of small lemons, were quite tender and remained enlarged and tender during the entire illness. At no time did any hemorrhages into the skin appear and hemorrhages into the mucous membranes were confined to those immediately adjacent

to areas of necrosis. Slight bleeding from the rectum occurred later, but the patient had had some recent trouble with hemorrhoids so that it was difficult to determine the exact source of this bleeding. The liver remained enlarged but at no time was the spleen felt and no lymph glands other than those of the neck were palpable. The patient had previously shown an idiosyncracy to Fowler's Solution so that neither this form of arsenic nor neoarsphenamine were used. She was given increasing doses of sodium cacodylate without any apparent effect. Later she received two small transfusions of citrated blood. Nine days after admission to the hospital signs of beginning consolidation appeared in the lower

TABLE I

	DIFFERENTIAL W.B.C. COUNTS							
	12–5–35	12–8–35	12–9–35	12–10–35	12–11–35	12–12–35	12–13–35	12–14–35
N. myelocytes	0.6	0.6	0.0	0.0	1.7	0.6	1.7	3.0
J. neutrophiles	1.0	1.0	1.7	1.5	1.7	0.6	1.7	0.7
Seg. neutrophiles	4.7	3.5	1.7	2.3	1.0	0.3	1.0	0.3
Eosinophiles	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0
Total	6.3	5.1	3.4	4.1	4.4	1.5	4.4	4.0
Young lymph	1.0	3.0	2.3	3.0	3.3	3.3	2.7	2.3
Adult lymph	0.8	3.2	2.0	2.3	2.3	2.6	2.0	3.7
Total	1.8	6.2	4.3	5.3	5.6	5.9	4.7	6.0
Monoblasts	6.5	4.0	9.3	16.3	10.5	13.5	8.3	7.3
Premonocytes	52.6	37.7	30.7	36.3	30.5	42.7	43.3	44.7
Monocytes	32.8	52.0	50.3	38.0	49.0	36.4	39.3	38.0
Total	91.9	88.7	90.3	90.6	90.0	92.6	90.9	90.0
W.B.C.	20150	25600	72400	60000	51650	62000	68000	76000

lobe of the left lung. The pneumonia rapidly progressed, extended to the opposite side, and the patient died thirty-six hours later on December 15, 1934, eleven days after admission to the hospital and sixteen days after the first appearance of acute symptoms. The results of the studies of the blood are shown in the accompanying table.

Autopsy

The autopsy (No. 13987) was performed 11 hours after death. The report has been abbreviated, but no pertinent observations have been omitted.

Body of a well developed and fairly well nourished adult white woman about 40 years of age. The skin appeared normal everywhere except over the forearms

where there were numerous petechial hemorrhages. These extended upward to a line just above the elbow on each side. In the conjunctiva of the right eye there were two minute petechial hemorrhages. The gums were greyish and necrotic in small patches, as described in the clinical history. No other significant abnormalities were made out in the external examination of the body.

The peritoneal cavity contained no excess fluid; its surfaces were smooth. The liver was enlarged, extending 7 cm. below the costal margin. The spleen was greatly enlarged, protruding prominently below the margin of the ribs for a distance of 8 cm. The pleural and pericardial cavities were normal.

The site of the *thymus* was occupied by a mass of fatty tissue. The *mediastinal and peribronchial lymph nodes* were slightly enlarged and rather soft. On their cut surfaces there were some poorly defined, greyish mottled areas visible against the black pigmented tissue.

The *heart* was essentially normal. The pleural surfaces of the *lungs* were smooth. On the cut surfaces of the lungs, small irregular patches of pneumonic consolidation surrounded by areas of hemorrhage were visible in the lower lobes. The remaining parts of the lungs were air-containing but very oedematous.

The *spleen* weighed 610 grams and measured 18 x 10 x 5.5 cm. Its capsule was smooth and tense. On the convex surface there were two irregularly outlined yellowish-grey infarcts, each measuring about 1 x 2 cm. The cut surface of the spleen bulged outward slightly. The tissue was rather soft and of a uniform greyish-red color. The Malpighian bodies could not be distinguished. Small, dark areas of necrosis, 1 to 3 mm. in diameter, were scattered at intervals through the splenic pulp.

The *liver* weighed 2315 gm. and measured 34 x 20 x 8.5 cm. It was soft and pale yellowish-brown in color. The lobules, as seen on the cut surface, appeared somewhat swollen. The periportal areas were just visible on close examination as greyish dots and lines. No abnormalities were found in the *pancreas*, but the fat around it contained many hemorrhages. The *stomach* and *intestines* appeared grossly normal. Peyer's patches and the solitary lymphoid follicles in the ileum and caecum were not unusually conspicuous. In the *rectum* just above the anal orifice there were two ulcers, each measuring 1 cm. in diameter. Their bases were slightly excavated and covered by an opaque, necrotic layer, while their margins were swollen and hemorrhagic.

The *mesenteric lymph nodes* were moderately enlarged and could be seen through the fat as deep red nodules. The *retroperitoneal lymph nodes*, especially those at the root of the mesentery and about the head of the pancreas, were even larger, measuring up to 3 cm. in diameter. All of these nodes were dark red, very soft and surrounded by hemorrhages in the retroperitoneal fat. The larger ones were almost completely occupied by the coalescent, mushy areas of necrosis and hemorrhage. Slightly smaller lymph nodes were mottled with hemorrhages scattered through the intact, soft pinkish-grey tissue. The *adrenal glands* were slightly enlarged. The medulla was dark red and very soft; the deeper layers of the cortex were closely flecked with hemorrhages.

The *kidneys* were alike and normal in size and shape. Their surfaces were smooth, but flecked with numerous petechial hemorrhages, which were closely placed throughout the thickness of the cortex. Smaller numbers of hemorrhages were scattered through the pyramids. The calyces of the kidney pelves showed solid patches of hemorrhage beneath their surfaces. The remainder of the pelves appeared normal, though the fat about them contained hemorrhages. The *ureters*, *bladder* and *urethra* presented no abnormalities. The mucosa of the *vagina* was smooth but diffusely reddened. Just within the external orifice of the vagina, there were several small ulcers, each about 1 cm. in diameter. Their margins were swollen and hemorrhagic, their bases covered by a layer of greyish-red necrotic tissue. The mucosa of the *uterus* was smooth and velvety but uniformly dark red in color. No other gross abnormalities were found in the uterus, tubes or ovaries.

The faucial and pharyngeal tonsils were not removed with the organs of the neck.

The *lingual tonsil* was conspicuously swollen, the tissue greyish-red on the cut surface. The *epiglottis*, the *aryepiglottic folds*, the *pyriform recesses* and the *pharyngeal walls* nearby were deep red, swollen and oedematous. Their surfaces were covered with a thin, greyish film which was loosely adherent. No deep ulcerations were seen. The *oesophagus*, *larynx* and *trachea*, the *thyroid* and the *parathyroid glands* presented no gross abnormalities.

The *bone-marrow* of the lumbar vertebrae and of the ribs was uniformly greyish-red. The upper half of the right femur, removed and split longitudinally, showed bone-marrow of a similar, greyish-red color in the head and neck, but in the upper end of the shaft, this merged into solid pale grey marrow. Further down, some patches of yellow fat appeared and these became increasingly large and abundant toward the middle of the shaft where the marrow was composed almost entirely of fat with only a few small areas of greyish opacity. The *voluntary muscles* were pale but appeared otherwise normal.

Permission for examination of the cranial cavity was not obtained.

A *postmortem culture* of blood from heart was sterile. In a culture from one lung, B. coli communis, Staphylococcus aureus and Alpha streptococcus salivarius, were present in large numbers.

Microscopical examination

Thin paraffin sections were cut from blocks of tissue fixed in Zenkerformol solution. In addition to those stained with hematoxylin and eosin, sections of all tissues which contained any noteworthy infiltrations of leukemic cells were stained with the Giemsa stain. Repeated efforts to demonstrate cells granules by means of Goodpasture's peroxidase stain were unsuccessful even in the case of mature polymorphonuclear leucocytes. Failure was apparently due to the fact that the tissues had been too long in the formalin fixative before the stains were attempted, for control stains on freshly fixed tissues gave brilliant results.

Examination of the Giemsa-stained sections showed that the leukemic infiltra-

tions in the various tissues were composed of a variety of types of cells. The few mature lymphocytes, plasma cells and polymorphonuclear leucocytes could be recognized easily. Typical megakaryocytes were conspicuous in most of the larger cell-accumulations, but the majority of the cells were immature forms. Among these, there were many unmistakable myeloblasts and myelocytes, and in addition, other cells which were regarded as of the monocytic variety. The latter were distinguished by the characteristics indicated in the following description.

Cells of the monocytic series. These cells had rather large nuclei which, when seen under the oil-immersion lens, almost always showed a considerable degree of

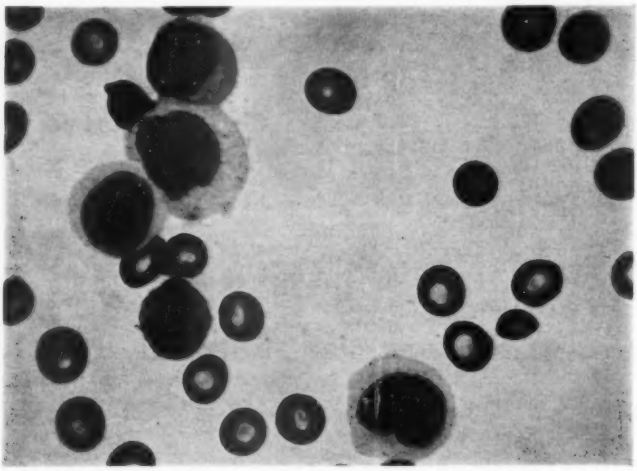

FIG. 1. SHOWING MONOCYTES IN THE CIRCULATING BLOOD IN VARYING STATES OF MATURITY

The largest and most mature monocyte shows the serrated border of the cell and a tendency to folding of the nucleus. A myelocyte is present in the field.

irregularity in outline. A few of the cells, thought to be the younger forms, had nuclei which were roughly oval but sharply indented at one or more points. Some nuclei were deeply indented in several places. The majority of the cells, however, had nuclei with very irregular outlines. These nuclei appeared to be folded upon themselves once or several times, so that the indentations in the nuclear margins were continued into the centers of the nuclei as narrow corrugations, the edges of which were traceable as clear refractive lines.

Such nuclei had a "crumpled" appearance. The nuclear membrane always showed up very distinctly as a thin, blue, highly refractive line, but the body of the nucleus was usually stained very lightly, without visible nucleoli. It appeared

practically homogeneous in the more mature cells with highly complicated nuclear outlines. Indeed, even in the younger cells with simpler nuclear form, only the finest stippling of the nucleus could be seen, although the nucleus as a whole was somewhat more deeply stained. The cytoplasm varied in abundance from cell to cell, but was usually rather voluminous. It was stained a pale pink or bluish-pink color. The cells margins were serrated or irregular and often difficult to distinguish. No distinct granules could be seen in the cytoplasm of any of the cells of this type in the tissue sections.[2]

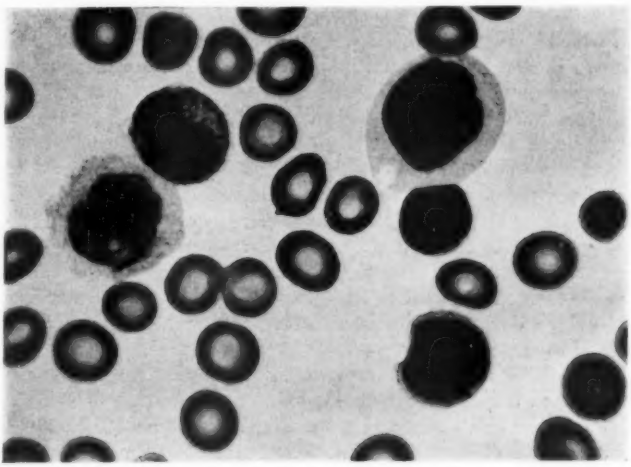

FIG. II. SHOWING TWO MATURE MONOCYTES, ONE WITH SERRATED BORDER AND A TENDENCY TO FOLDING OF THE NUCLEUS, AND THE OTHER WITH A DIGESTION VACUOLE IN THE CYTOPLASM

A myelocyte is present in the field and the two more immature cells are immature monocytes.

Cells of the myeloid series. Myeloblasts were distinguished by a number of features contrasting with those described as characteristic of the monocytes. Their nuclei varied somewhat in size but were generally round or oval in outline without any irregularities in their contours. Occasional cells showed shallow concavities in their nuclei, but such irregularities were almost always smoothly

[2] Through the kindness of Dr. P. W. Clough, we were able to corroborate our identification of the monocytic cells by comparison with those in the tissues of his case of monocytic leukemia (*Bull. Johns Hopkins Hosp.*, 1932, **51**, 148), in which cells of the monocytic type formed the majority both in the blood and in the organs.

rounded. The deep blue staining nuclear membrane gave the impression of being thicker and less refractive than that of the monocytes. The nuclei showed a definite internal architecture. The chromatin was distributed in fine threads with conspicuous deep blue knots of chromatin at one or several points. In addition, a finer stippling of the nucleus was usually visible, especially in a narrow zone near the periphery. Two to four nucleoli could be distinguished in the nuclei of many, if not most, of the cells. The cytoplasm was rather scanty, smoothly outlined, moderately basophilic and devoid of granules. The identification of these cells as myeloblasts was rendered more certain by careful comparison with the leukemic cells in the tissue sections from typical cases of acute myeloid leukemia, and by comparison with the myeloblasts in sections of normal bone marrow.

The nuclei of the myelocytes were, on the whole, slightly smaller but possessed the same general characters as those of the myeloblasts. The cytoplasm was somewhat more abundant, less basophilic, and filled more or less completely with rather coarse neutrophilic or eosinophilic granules. No basophilic myelocytes were seen.

The greater proportion of the cells in process of mitotic division possessed a moderately basophilic cytoplasm, lacking in granules and identical in appearance with the cytoplasm of the myeloblasts. But many of the dividing cells had a paler cytoplasm which contained distinct coarse, neutrophilic granules, or in a smaller number of cells, brilliantly stained eosinophilic granules. Such granular cells in mitosis were found in all the organs examined. The mitotic figures were frequently irregular or asymmetrical.

Differential cell-counts. In order to determine with some degree of accuracy the relative numbers of the different kinds of cells found infiltrating the tissues, differential counts were made in sections of various organs stained with the Giemsa stain. Under the oil-immersion lens, the microscopical slide was moved in a straight line by means of a mechanical stage, while a fine hair, fixed in the ocular lens, served as a pointer. Those cells upon which the tip of the pointer fell were identified and counted, up to a total of 500 cells in each organ. All nucleated cells, with exception of tissue cells, were included in the counts. The figures obtained in this way are given in Table II. A very few cells were encountered which had an indifferent appearance, possessing some of the characters of young monocytes and some features resembling those of myeloblasts. Such doubtful cells were classified as cells of the monocytic series, so that all cells recorded in other categories represent unmistakable cells of the type designated. No attempt was made to classify the monocytic cells as monoblasts, premonocytes or monocytes, but most of these cells appeared to be relatively mature.

Duplicate counts of 500 cells each were made in different sections (serial) of the liver and bone marrow of the shaft of the femur. The close correspondence between the figures obtained in each case, as shown in the table, indicates that 500 cells constitute a sufficiently large sample to yield a reasonably reliable result, at least as regards the proportion between monocytes and the total number of immature myeloid cells. In all instances, the results of the differential counts

TABLE II

Differential cell-counts in tissue sections

	MONOCYTIC CELLS	TOTAL IMMATURE MYELOID CELLS	MYELOBLASTS	NEUTROPHILE MYELOCYTES	EOSINOPHILE MYELOCYTES	POLYMORPHONUCLEAR LEUCOCYTES	MITOTIC FIGURES	MEGAKARYOCYTES	LYMPHOCYTES	PLASMA CELLS	MEGALOBLASTS	NORMOBLASTS
Bone marrow shaft of femur	48 9.6%	84.0%	328 65.6%	57 11.4%	35 7.0%	4 0.8%	4 0.8%	6 1.2%	3 0.6%	0 0%	12 2.4%	3 0.6%
Bone marrow shaft of femur (duplicate)	43 8.6%	84.4%	282 56.4%	69 13.8%	71 14.2%	8 1.6%	3 0.6%	2 0.4%	6 1.2%	1 0.2%	11 2.2%	4 0.8%
Bone marrow vertebra	45 9.0%	82.6%	332 66.4%	54 10.8%	27 5.4%	4 0.8%	7 1.4%	5 1.0%	4 0.8%	4 0.8%	13 2.6%	5 1.0%
Spleen	114 22.8%	69.8%	275 55.0%	42 8.4%	32 6.4%	5 1.0%	7 1.4%	5 1.0%	11 2.2%	4 0.8%	4 0.8%	1 0.2%
Retroperitoneal lymph node	111 22.2%	69.2%	201 40.2%	104 20.8%	41 8.2%	14 2.8%	2 0.4%	3 0.6%	22 4.4%	2 0.4%	0 0%	0 0%
Liver periportal infiltrations	121 24.2%	60.6%	201 40.2%	80 16.0%	22 4.4%	8 1.6%	5 1.0%	3 0.6%	53 10.6%	7 1.4%	0 0%	0 0%
Liver periportal infiltrations (duplicate)	115 23.0%	63.2%	204 40.8%	96 19.2%	16 3.2%	9 1.8%	3 0.6%	4 0.8%	48 9.6%	5 1.0%	0 0%	0 0%
Kidneys	69 13.8%	71.4%	276 55.2%	47 9.4%	34 6.8%	4 0.8%	5 1.0%	8 1.6%	55 11.0%	2 0.4%	0 0%	0 0%
Blood in blood vessels	214 42.8%	51.0%	194 38.8%	37 7.4%	24 4.8%	10 2.0%	0 0%	0 0%	21 4.2%	0 0%	0 0%	0 0%
Blood in blood vessels (duplicate)	227 45.4%	48.8%	177 35.4%	50 10.0%	17 3.4%	7 1.4%	1 0.2%	0 0%	20 4.0%	0 0%	0 0%	1 0.2%

Each count and duplicate count totals 500 cells. For the sake of easy comparison with the number of monocytic cells, the percentage of the total formed by immature myeloid cells has been placed in the second column. Column 2 is, therefore, merely the sum of columns 3, 4 and 5.

correspond with the general impression gained by careful inspection of wide areas of the tissues under the oil-immersion lens.

The blood, lying in blood vessels throughout the various tissues, contained large numbers of nucleated cells, among which cells of the monocytic variety were present in considerably larger proportion than in any of the organs. For purposes of more accurate comparison differential counts of these nucleated cells in the blood were made, using the same method of counting and the same criteria of differentiation as were applied in recording the cells found in the tissues. The results of two counts of 500 cells each are included in the table.

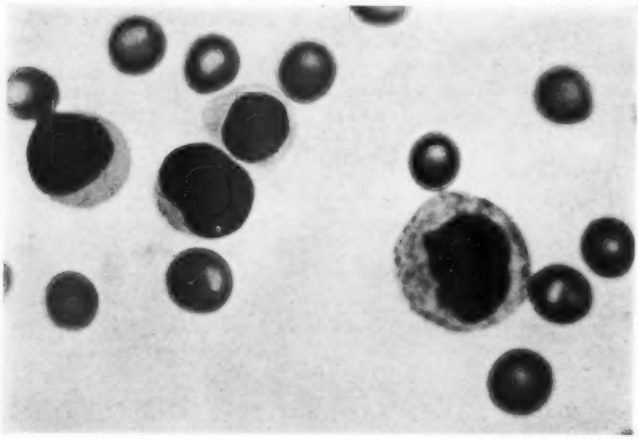

FIG. III. SHOWING A MATURE MONOCYTE IN THE CIRCULATING BLOOD WITH FINE GRANULATION IN THE CYTOPLASM AND FOLDING OF THE NUCLEUS

The small white cell with a darkly stained nucleus is a lymphocyte and the two remaining white cells are immature monocytes.

Microscopical note. The general distribution of the leukemic infiltrations as well as the character of other lesions may be indicated briefly.

The *bone-marrow* of one of the lumbar vertebrae was composed of solid masses of cells which filled the marrow spaces completely. By far the greater proportion of the cells were of the myeloid series. The different types of myeloid cells were distributed fairly uniformly, but there were occasional clumps consisting mostly of neutrophilic and eosinophilic myelocytes. Monocytes occurred in no special relationship to other cells in the bone marrow. Mitotic figures and megakaryocytes were scattered at intervals through the tissue. Megaloblasts and normoblasts were extremely few as compared with normal marrow. The bone marrow of a rib was practically indistinguishable from that of the vertebrae. Bone mar-

row from the shaft of the femur presented essentially the same appearance as that of the vertebrae and rib except for the presence of scattered islands of fatty tissue.

The *spleen* was packed uniformly with immature myeloid cells and a smaller proportion of more or less mature monocytes. There was no noticeable grouping of particular types of cells. No changes were observed in the endothelial cells lining the sinuses which could be interpreted as evidence of the origin of monocytes from this source, nor were such changes observed in any of the other organs. The normal architecture of the spleen was greatly distorted. The Malpighian bodies were practically obliterated. In addition to the large infarcts already mentioned, there were many minute focal areas of necrosis and hemorrhage scattered through the splenic pulp.

The larger *retroperitoneal lymph nodes* were almost completely occupied by areas of necrosis and hemorrhage. In the smaller ones, the lymph nodules about the periphery could be distinguished in places, but for the most part the tissue was packed solidly with masses of myeloblasts, myelocytes and monocytes. There were scattered necroses and hemorrhages.

In the sections of *liver*, the portal spaces were full of infiltrating cells but none of these areas was larger than a low power field. The small number of lymphocytes mixed with the other cells presumably corresponded with those found normally in the portal spaces. The differential cell-counts were confined to cells in the periportal infiltrations, but the sinusoids of the liver also contained many myeloblasts, myelocytes and monocytes together with particularly large number of megakaryocytes. As many as 15 or 20 of these were counted in the sinusoids of single liver lobules in the sections, although a number between 5 and 10 was more frequently found.

In the *kidneys* numerous small leukemic infiltrations were scattered through the cortex. Larger infiltrations were distributed about the blood vessels between the cortex and medulla. Some of these were larger than a low power field. Toward the centers of such nodules, the tubules were represented by necrotic remnants, surrounded frequently by many scattered lymphocytes. The differential count of the infiltrating cells in the kidney was made in areas of this description.

Other tissues in various parts of the body contained more or less abundant accumulations of infiltrating cells. These consisted for the most part of myeloblasts together with neutrophilic and eosinophilic myelocytes. Monocytic cells were always present, though in relatively small proportion, approximating that in which they occurred in the kidneys. Mitotic figures were found even in some of the smallest accumulations of cells, but megakaryocytes were generally observed only in the larger infiltrations.

The leukemic cells showed a marked tendency to encircle minute blood vessels and to spread more or less widely from such foci into the surrounding tissue. The particular distribution was found in the retroperitoneal and mediastinal fat, the adrenals and lungs. The lymphoid follicles in Peyer's patches and in the appendix were slightly infiltrated, the mediastinal lymph nodes were partly filled with infiltrating cells, while the lingual tonsil was almost completely replaced. The

atrophied remnants of the thymus were surrounded by narrow zones of cells. The mucosa of the uterus was full of infiltrating cells with confluent small hemorrhages. There was a zone of infiltration about a degenerating corpus luteum in one ovary.

The necrotic superficial layers of the ulcers in the pharynx, rectum and vagina contained clouds of bacteria of various kinds. The bases of the ulcers were densely infiltrated with leukemic cells but scarcely any mature polymorphonuclear leucocytes could be found. The pulmonary alveoli in the areas of pneumonic consolidation were filled with immature myeloid cells and rather large numbers of monocytes, some of them containing dust particles. Clumps of Gram-positive cocci were scattered throughout, and clouds of similar organisms were found in the

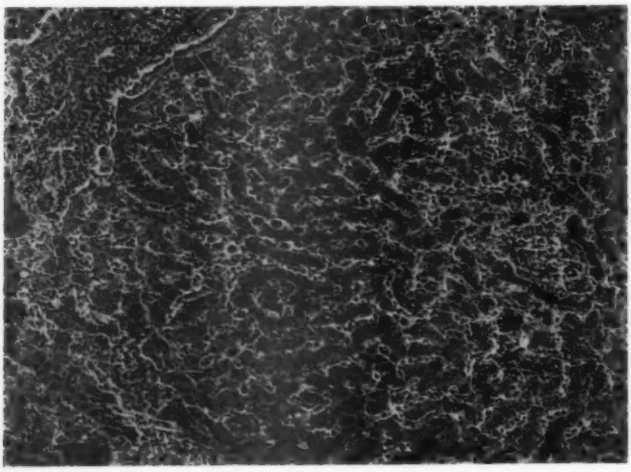

FIG. IV. SHOWING THE LEUKEMIC INFILTRATIONS IN THE PORTAL SPACES OF THE LIVER, AND SEVERAL MEGAKARYOCYTES IN THE SINUSES

bronchi. There was no leucocytic reaction except in the bronchial lumina where mature polymorphonuclear leucocytes were mixed in large numbers with the immature forms.

Microscopical sections of the heart, thyroid and parathyroid glands, stomach, pancreas, urinary bladder, voluntary muscle and skin revealed no significant lesions.

DISCUSSION

We are, then, reporting a case of leukemia which ran a particularly acute course, the total duration being, as far as we could tell from

symptoms, sixteen days. The clinical features in the main were strikingly similar to those set apart by Forkner as characteristic of acute monocytic leukemia. The onset was fairly acute with fever, malaise, fatigue and body aching. The hyperplasia of the lymphoid tissue in the pharynx was early and ulceration of the gums, buccal mucous membrane and pharyngeal tissues soon followed. The hemorrhagic manifestations were relatively slight and confined to the periphery of these lesions, whereas the development of necrosis and ulceration was prompt and extensive. The swelling of the gingival lesions was prominent, the gums reaching to the level of, and in places protruding beyond, the cutting margins of the teeth. The superficial cervical lymph nodes were enlarged and there was, therefore, neither the absence of lymph node enlargement, so common in acute myeloid leukemia, nor the slight though general enlargement seen in acute lymphatic leukemia. The liver was palpably enlarged and was found at autopsy to weigh 2300 grams. Though the spleen measured 18 x 10 x 5.5 cm. it was not felt during life. During the entire illness abdominal distention was prominent and this may have accounted for our inability to feel the spleen.

Cells classed as those of the monocytic series predominated in the circulating blood and were strikingly constant in their proportion during the entire illness. They varied from 88 to 92 per cent, although the total white blood cell count varied from 20,000 on admission to the hospital to 76,000 on the day before death. All transitions from monoblasts to mature monocytes were present. However, in this, as in other reported cases, there was evidently a terminal outpouring of myeloid cells into the blood stream. This is apparent when comparison is made between the last differential count of the white cells in blood smears and the differential counts of the white cells lying in blood vessels in the tissue sections taken after death, which occurred some 36 hours later. Eosinophilic granulocytes, which are quite as unmistakable in tissue sections as in blood smears, rose from 0 to 4.1 per cent, while other cells of the myeloid series, especially myeloblasts, increased in an equally striking proportion, so that the total of monocytic cells was reduced to only 44.1 per cent.

Is this sufficient basis for regarding monocytic leukemia as an entity, distinct from other types of leukemia? We have presented

here a case of acute leukemia with all of the clinical and hematological characteristics that one would expect in a case in which the monocyte was the leukemic cell. The histological study, however, disturbs the acceptance of the view that this is a case of true monocytic leukemia. In lymphoid and myeloid leukemia the tissue infiltrations are composed practically completely of the characteristic cell type and hyperplasia of the tissues producing the characteristic cell type completely overshadows hyperplasia of tissues producing other types of blood cells. Such, however, is not the case here, nor has it been so in the other reported cases of so-called monocytic leukemia. In all of the reported cases many cells resembling monocytes have been found in the tissues, chiefly in the liver, spleen and lymph glands. In none, however, has there been any accurate estimation of the proportion of monocytic cells in the tissues. Only by means of such counts can one obtain an accurate impression of the type of cell present. The desirability of this type of study is further indicated by the fact that in so few of the cases of "monocytic leukemia" does the proportion of monocytic cells present in the tissues even approach the degree of type cell infiltration seen in either lymphoid or myeloid leukemia. Furthermore, in many of the cases some degree of myeloid hyperplasia is reported and in others late outpourings of granulocytes in the blood stream have been observed, and in still others the tissue response to extensive circulatory monocytosis has been practically entirely myeloid.

We find in the present case that there are many cells of the monocytic type in the tissues, but we have found nothing to suggest "endothelial hyperplasia," mentioned by some authors. There was in addition definite myeloid hyperplasia in the bone marrow. When we apply a quantitative estimation of the cells infiltrating the tissues we obtain the results shown in Table II, and it is to be noted that most of these are immature myeloid cells, the majority of which are myeloblasts. Of the cases more fully described, that of Clough, whose sections we have had an opportunity to examine, probably shows the greatest amount of infiltration of monocytic cells. It conforms more nearly to the criteria prescribed for monocytic leukemia, although myeloid cells were present and described as "a few myelocytes and myeloblasts."

We have recently observed a case of acute leukemia in which the

white cells of the blood numbered 26,000, 49 per cent of which were monocytic cells. This case also showed the necrosis and ulceration of the mucous membrane of the mouth stressed by Forkner as characteristic of monocytic leukemia. At autopsy the hyperplasia and tissue infiltration found was practically entirely myeloid and the case falls into that group which Gittins and Hawksley describe as monocytosis but with tissue infiltrations that are purely myeloid in type. It would seem, then, that the present case occupies an intermediate position with that of Clough at one extreme and the case just mentioned at the other.

One also must consider the fact that at times megalokaryocytes are seen in the tissue infiltrations of myeloid leukemia and they were present in all of the tissues studied in this case. In addition to megalokaryocytes one at times sees monocytes in the infiltrations associated with the typical blood picture of myeloid leukemia. In such instances it would seem that the variation is the reverse of that seen in the present case.

It is evident that transitions occur in this type of leukemia and it is difficult to apply the criteria rigidly when such a pronounced variation in the myeloid response, so regularly present, occurs. The marked myeloid infiltrations in the present case suggest that myeloid tissue plays more than an accidental rôle in the disease process. It would be tempting to speculate that blast cells, certainly so far as myeloblasts and monoblasts are concerned, are closely allied histogenetically and that the contention of some that the point at which cell types become irreversible is not far removed from the blast stage is probably correct. We are not attempting to say at what point this differentiation occurs, but do feel that the consistent myeloid response in "monocytic leukemia" cannot be ignored, and make a plea for more accurate determination of the type and number of cells involved in the tissue response in "monocytic leukemia." We desire also to stress the apparent transition which exists, in which the present case would occupy an intermediary position. This case, as have many similar ones, shows all of the features which Clough and others have indicated should characterize "monocytic leukemia," but the myeloid hyperplasia and infiltrations cause one to hesitate in classifying it as a pathologic entity. Clinically, it is a typical case of "monocytic

leukemia," but histologically the myeloid hyperplasia far outweighs the monocytic response. There is no objection, so far as we can see, to calling these cases monocytic leukemia, but it must be understood that we are so doing on a clinical and hematological basis and are mindful of the varied tissue responses which occur, and which we believe require more careful study than has been given them in the past.

SUMMARY

A case of acute leukemia is presented which fulfills all of the clinical and hematological requirements of the diagnosis, "monocytic leukemia." However, the hyperplasia and tissue infiltrations show both myeloid and monocytic response, the former much in excess of the latter.

All transitions in the amount of myeloid response occur in "monocytic leukemia," and this type of response is so regular as to suggest that myeloid tissue plays more than an accidental rôle in the disease process.

The present case occupies an intermediate position, with those cases in which monocytic response predominates at one extreme and those in which the hyperplasia and tissue infiltrations are entirely myeloid at the other.

REFERENCES

(1) Downey, H.: The occurrence and significance of the "myeloblast" under normal and pathological conditions. *Arch. Int. Med.*, **33**, 301, 1924.

(2) Bloom, W.: The origin and nature of the monocyte. *Folia haemat.*, **37**, 1, 1928.

(3) Sabin, F. R., Doan, C. A., and Cunningham, R. S.: Discrimination of two types of phagocytic cells in the connective tissue by the supravital technique. *Contrib. to Embryol., No. 84, Carnegie Inst. of Washington*, **16**, 125, 1925.

(4) Cunningham, R. S., Sabin, F. R., and Doan, C. A.: The development of leucocytes, lymphocytes, and monocytes from a specific stem cell in adult tissues. *Ibid.*, **16**, 229, 1925.

(5) Naegeli, O.: Blutkrankheiten und Blutdiagnostik. J. Springen, Berlin, V. Auf., 1931.

(6) Reschad, H., and Schilling, V.: Über eine neue Leukämie durch echte Übergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen. *Münch. med. Wchnschr.*, **60**, 1981, 1913.

(7) RICHTER, M. N.: The origin and development of monocytes in monocytic leukemia. *Arch. of Pathol. and Lab. Med.*, **1**, 841, 1926.
(8) DAMESHEK, W.: Acute monocytic (histiocytic) leukemia. *Arch. Int. Med.*, **46**, 718, 1930.
(9) ROSENTHAL, N.: Some atypical cases of leukemia. *M. Clin. North America*, **4**, 1607, 1921.
(10) FARLEY, D. L.: Monocytic leukemia. *Ibid.*, **13**, 991, 1929.
(11) COOKE, W. E.: Acute monocytic (histiocytic) leukemia. *Lancet*, **2**, 129, 1931.
(12) CLOUGH, P. W.: Monocytic leukemia. *Bull. Johns Hopkins Hosp.*, **51**, 148, 1932.
(13) SYDENSTRICKER, V. P., AND PHINIZY, T. B.: Acute monocytic leukemia. Case with partial autopsy. *Am. J. Med. Sci.*, **184**, 770, 1932.
(14) ORR, J. W.: Monocytic leukemia. *Lancet*, **1**, 403, 1933.
(15) FORKNER, C. E.: Clinical and pathological differentiation of the acute leukemias, with special reference to acute monocytic leukemia. *Arch. Int. Med.*, **53**, 1, 1934.
(16) DOAN, C. A., AND WISEMAN, B. K.: The Monocyte, Monocytosis, and Monocytic Leukosis, a clinical and pathological study. *Ann. of Int. Med.*, **8**, 383, 1934.
(17) GITTENS, R., AND HAWKSLEY, J. C.: Reticulo-endotheliomatosis, ovarian endothelioma and monocytic (histiocytic) leukemia. *J. Path. and Bact.*, **36**, 115, 1933.
(18) FOORD, A. G., PARSONS, L., AND BUTT, E. M.: Leukemic reticulo-endotheliosis (monocytic leukemia). *J. A. M. A.*, **101**, 1859, 1933.
(19) WHITBY, L. E. H., AND CHRISTIE, J. M.: Monocytic Leukemia. *Lancet*, **1**, 80, 1935.

THE EXPERIMENTAL PRODUCTION OF WHOOPING COUGH IN CHIMPANZEES[1]

ARNOLD R. RICH, PERRIN H. LONG, J. HOWARD BROWN, ELEANOR A. BLISS AND L. EMMETT HOLT, JR.

(From the Departments of Pathology and Bacteriology, Medicine and Pediatrics, and the Biological Laboratory of the John J. Abel Fund for Research on the Common Cold, Johns Hopkins University Medical School, Baltimore, Md.)

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It is now generally accepted that the Bordet-Gengou bacillus plays an important rôle in the etiology of whooping cough, and with very good reason. The bacillus can be cultivated from the respiratory secretions of patients with great regularity in the early stages of the disease, though with diminishing frequency thereafter; at autopsy the organisms may be found in great numbers entangled in the cilia of the respiratory tract; and specific complement-fixing antibody can usually be demonstrated as the disease progresses.

Although most observers have been willing to concede that this organism is the sole cause of the disease, others have remained skeptical; and there is no doubt that certain facts remain to be explained, and certain possibilities to be tested, before the Bordet-Gengou bacillus can unreservedly be regarded as solely responsible for the disease. Reasons for questioning the exclusive rôle of this bacillus in the pathogenesis of pertussis have been discussed elsewhere in some detail by one of us (1), and need be only briefly mentioned here.

Animal inoculations with pure cultures of this bacillus have given results which are far from satisfactory. In the great majority of experiments the introduction of the bacilli into the respiratory tract has produced either no result whatever or else symptoms bearing no close resemblance to whooping cough (4). Several observers (2) have, however, reported the production of a cough by this means,

[1] Aided by a grant from the Chemical Foundation and a donation from Mr. Roswell Miller, Jr., and by a grant from the Ella Sachs Plotz Fund.

but a severe and protracted cough has likewise been produced by similar inoculation with other bacteria (5). The most successful inoculations with Bordet-Gengou bacilli were those of Sauer and Hambrecht (3) in monkeys, but it was only in seven out of seventy-five attempts in which pure cultures alone were used that a cough was produced, and then only by forcing large quantities of bacilli directly into the trachea. In only three of the seven coughing animals did the lymphocytes rise well above their original level, in no case surpassing the upper limits of normal found by these investigators in control animals.[2]

In 1903, Arnheim (13) clearly described the clustering of minute, Gram-negative bacilli in the cilia of the respiratory tract in pertussis; and in 1912, Mallory and his associates (4) re-emphasized this peculiar bacterial localization which has since been regarded as pathognomonic of the disease. While it is altogether likely that the paroxysmal cough in pertussis is due to the irritative action of the bacteria localized in the cilia of the respiratory tract leading to the production of plugs of tenacious secretion, there is now evidence that this bacterial localization is not specific for the Bordet-Genou bacillus. It is known that in canine distemper Bacterium bronchisepticum, also a minute, Gram-negative, organism, may be found similarly localized in the cilia; and Rich (1) has recently demonstrated that in man the influenza bacillus, another mi ute, Gram-negative, bacillus, also tends to localize in this site. It is well known that influenza bacillus infections of the upper respiratory tract may at times be accompanied by a paroxysmal cough indistinguishable from that of pertussis (6); and such a cough has also been observed in human infection with Bacterium bronchisepticum (7). Since both of the latter organisms are indistinguishable morphologically from the Bordet-Gengou bacillus in histological sections, it is clear that the presence of minute, Gram-negative, bacilli entangled in the cilia of the respiratory tract in per-

[2] More recently, Culotta, Harvey and Gordon (12) have produced a pertussis-like syndrome in 3 out of 19 experiments in which large doses of Bordet-Gengou bacilli were injected directly into the trachea. Intratracheal injection of unfiltered nasal washings from human cases of pertussis gave negative results. They conclude that the monkey is not a satisfactory animal for the experimental study of whooping cough.

tussis is insufficient proof that the bacteria are Bordet-Gengou bacilli, and this particularly since the influenza bacillus can commonly be cultivated, often in pure culture, from the trachea and bronchi in fatal cases of whooping cough. Indeed, one point which has led many to question the essential rôle of the Bordet-Gengou bacillus in pertussis is the fact that it can rarely be recovered from patients in the later stages of the disease, although the cough continues unabated. During this period, on the other hand, influenza bacilli are frequently present in abundance.

At the least, the above considerations hardly permit us to regard Koch's postulates as having been satisfyingly fulfilled in relation to the Bordet-Gengou bacillus and pertussis.

The view that a filterable virus may be the primary agent in pertussis, and that the Bordet-Gengou bacillus acts as an associated invader, has been expressed for some years in the German literature (8). It is a well known fact that interstitial mononuclear-cell infiltration of the bronchial wall, which occurs characteristically in pertussis, is likewise characteristically found in connection with virus diseases that affect the respiratory tract—*e.g.*, influenza and measles. Although this reaction has been attributed to a peculiarity of the secondary invaders or their toxic products, it is worthy of note that it has been readily produced experimentally by filterable viruses in the absence of bacteria (9). Furthermore, MacCallum has described the interstitial reaction in cases of human influenza in which the secondary invader was the pneumococcus (10), an organism which certainly does not ordinarily produce this type of reaction when acting alone.

It is true, however, that mononuclear infiltration of the bronchial walls is commonly encountered in subacute and chronic bacterial infections of the lungs or bronchi, regardless of the etiology, and it is undoubtedly possible that in pertussis it may represent a result of the long-continued bronchial infection; or, indeed, it may be a specific effect of the Bordet-Gengou bacillus itself without regard to chronicity.

The finding of intranuclear inclusion bodies in the pulmonary alveolar epithelium in pertussis by Feyrter (11) and, more recently, by McCordock (20) and Rich (1), has been interesting in relation to the view that a filterable virus may play a rôle in the etiology of pertussis, though the significance of these inclusions is still open to

question. The possibility that they may be the result of the aspiration of herpetic or of some other virus has been stressed by Rich (1). It is undoubtedly true that inclusion bodies are found in the lungs much more frequently in association with pertussis than in cases without pertussis, but it must be remembered that pertussis, with its paroxysmal coughing and vomiting and its inspiratory whoop, provides an unparallelled opportunity for aspiration of material from the mouth into the lung, especially in very young children. The fact that inclusions are much more rarely found in cases of non-pertussis pneumonia than in cases of pneumonia occurring in association with pertussis is, therefore, not very pure evidence that the virus responsible for the inclusions is a specific virus of pertussis. It may be remarked that Farber and Wolbach (18) have recently found exactly similar inclusion bodies in the parotid glands of 12 per cent of 183 unselected children studied at autopsy. Whether the virus responsible for these parotid gland inclusions is that of herpes or of some other virus has not yet been determined, but the frequency of their occurrence is impressive, and the opportunity of aspirating the particular causative virus with the saliva during the inspiratory whoop in pertussis is obvious. Whatever the agent responsible for the pulmonary inclusion bodies in pertussis may be, it is interesting to note that, even if it reaches the lung by aspiration, it may also become widely diffused throughout the body by way of the blood stream, for in three of five cases of pertussis in which we have recently found pulmonary intranuclear inclusions, precisely similar inclusions were present in the renal epithelium as well.

As a rule to which there are some exceptions, diseases caused by filterable viruses are characterized by a high degree of contagiousness and a durable immunity. Both of these characteristics are encountered in pertussis, but since some bacterial diseases are also highly contagious and confer a durable immunity, these characteristics can only be regarded as suggestively compatible with a virus etiology.

Likewise, the frequent complication of "encephalitis" without locally demonstrable bacteria in pertussis has suggested the presence of an invisible virus. It may be pointed out, however, that the "encephalitis" of pertussis does not resemble that which occurs as a complication of measles, vaccinia or varicella, and that clinical "en-

cephalitis" in pertussis may be represented pathologically by a variety of different lesions. We have recently had occasion to study histologically 12 cases of pertussis in which the diagnosis of pertussis encephalitis was made during life. One of these cases (Autopsy No. 10462) showed widespread loss of cortical cells with gliosis and great shrinkage of the brain; one (Autopsy No. 10564) showed a true encephalitis of marked degree, with abundant perivascular mononuclear-cell infiltration and small foci of necrosis with polymorphonuclear infiltration, the lesions being especially prominent in the basal ganglia and pons; in 4 cases (Autopsies 13429, 11019, 12734, 9011) there were only scattered petechial haemorrhages in the brain, cord or meninges; and in one case (Autopsy 14017) there was an organizing subdural blood clot with recent fresh haemorrhage. In the remaining 5 cases no lesions of any sort were found in the central nervous system. The petechial haemorrhages and the subdural haematoma may well have been mechanical results of the severe paroxysms of coughing. There are other cases in the literature in which a widespread loss of cortical cells, similar to that in the case mentioned above, occurred in association with pertussis (16). The relation of the case of inflammatory encephalitis in the above mentioned series to the cases in which cortical destruction was found is at present problematical. Certainly the localization of the lesions was very different in these two different types of damage. At all events, clinical symptoms of "encephalitis" occurring during pertussis may be caused by a variety of pathological alterations, and do not represent the effect of a single, specific form of lesion.

In recent years, a number of diseases once thought to be due to known micro-organisms have been found on closer study to have a dual etiology (1) a specific filterable virus which excites infection and paves the way for (2) a concomitant bacterial invader which is responsible for many of the symptoms. Demonstrated examples of such diseases are canine distemper (filterable virus commonly associated with Bact. bronchisepticum), hog cholera (filterable virus commonly associated with Bact. suipestifer) and swine influenza (filterable virus associated with H. influenzae suis (9)). In all probability, human influenza belongs in this group of virus-bacterial diseases. It was to test the attractive hypothesis that pertussis might

belong in this group of diseases with a dual etiology, that the present studies were undertaken. We were encouraged to test this possibility because of the fact that in one of the above-mentioned virus-bacterial diseases, canine distemper, natural infection with the virus is ordinarily followed by the colonization of minute Gram-negative bacilli (Bact. bronchisepticum) in the cilia of the respiratory tract, precisely as the Bordet-Gengou bacillus is found in pertussis, and that human infection with Bact. bronchisepticum has produced a pertussis-like cough (7). Furthermore, Bact. bronchisepticum was long regarded as the sole cause of canine distemper, and on even better experimental evidence than that upon which the belief that the Bordet-Gengou bacillus is the sole cause of whooping cough has rested.

EXPERIMENTS

In our experiments chimpanzees were used because of the well known susceptibility of these animals to human infectious diseases. In all, 17 experiments were carried out on 13 animals. The animals were kept in strict isolation, and rigorous precautions were exercised by attendants and observers to prevent cross infection. In each experiment in which filtered or unfiltered pertussis tracheal exudate was inoculated, the material was obtained from a different human subject during the first week of the cough. In every case the child from whom the material was obtained progressed through the typical course of whooping cough. All filtrates used were proved to be sterile for both aerobic and anaerobic bacteria. All were planted upon Bordet-Gengou medium, upon 5 per cent rabbit's blood dextrose agar plates, and in rabbit's blood and Smith-Noguchi medium. Each time that an ape was inoculated intra-orally or intranasally with test material, two other normal apes were given a control inoculation of the same amount of broth in the same manner. No symptoms of any sort followed any of the control inoculations.

The medium referred to throughout this paper for the isolation and cultivation of the Bordet-Gengou bacillus, whether on plates or on slants, was Bordet-Gengou glycerin potato agar containing about 50 per cent of defibrinated rabbit blood. The organism was recognized by its morphology, growth requirements, characteristic hemolytic colonies and inability to reduce nitrate or produce indol.

The protocols of the individual experiments are given below.

Experiment 1 (Ape "Joan"). In this experiment unfiltered exudate which had been coughed into a sterile container by a child with early whooping cough five hours previously was mixed with 10 cc. yeast infusion broth, and 6 cc. of this mixture was instilled into the mouth of a normal chimpanzee through a medicine dropper. Cultures of the material inoculated failed to show Bordet-Gengou bacilli. On the third day following the inoculation this ape developed a slight upper respiratory catarrh characterized by a scant nasal discharge and fever but without leucocytosis. The condition lasted for eight days and then disappeared· no cough developed. Complement fixation for the Bordet-Gengou bacillus was found to be positive 4 months after the original inoculation (see Chart I).

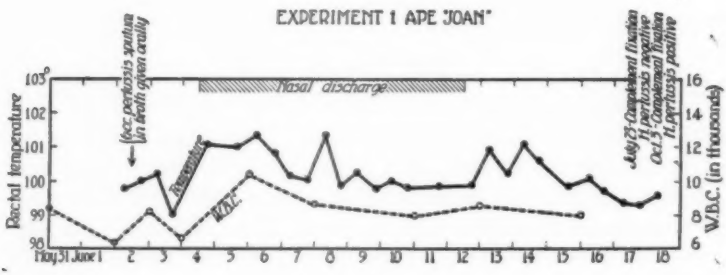

CHART I

Experiment 2 ("Ape III"). This normal animal was also inoculated with unfiltered material from a child with early whooping cough, but this time the material was aspirated through a bronchoscope directly from the trachea, and was promptly mixed with 25 cc. yeast infusion broth, and 10 cc. were gently instilled into the mouth of the ape. Bordet-Gengou bacilli were cultured from this material. After an incubation period of two days this ape developed a nasal discharge. The temperature on one occasion rose to 102°F. and the white blood cells to a maximum of 29,000 (the maximum lymphocyte count being 9,500). Within 5 days this catarrhal infection had cleared, but it returned again on the 24th day after inoculation; a cough was noted on the 31st day which soon became paroxysmal in character, lasting for about seven weeks; there were râles throughout the lungs at the height of this process (42nd to 52nd day). The animal developed a marked lymphocytosis (33,000). Cough plates contained many colonies of Bordet-Gengou bacilli and the complement fixation reaction became positive (49th day). The cough gradually disappeared and the leucocytes returned to their normal level (see Chart II).

Both of these apes, then, which were inoculated with unfiltered exudate from early cases of whooping cough, developed a catarrhal condition similar to that occurring at the onset of pertussis; but in addition one of them developed a severe, protracted paroxysmal cough accompanied by lymphocytosis. In all essential respects the disease 'whooping cough' was reproduced in this animal.

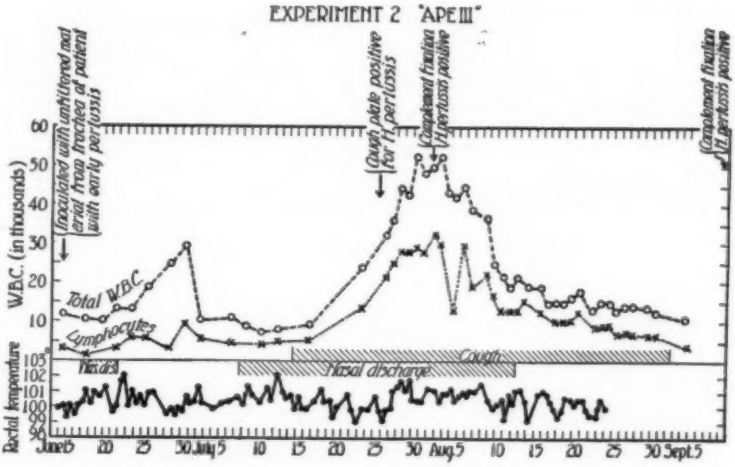
EXPERIMENT 2 "APE III"
Inoculated with unfiltered nasal fluid from tracheal exudate of patient with early pertussis
(Cough) date positive for H. pertussis
(Complement fixation H. pertussis positive
(Complement fixation H. pertussis positive
W.B.C. (in thousands)
Total W.B.C.
Lymphocytes
Nasal discharge
Cough
Rectal temperature
June 5 10 15 20 25 30 July 5 10 15 20 25 30 Aug. 5 10 15 20 25 30 Sept. 5

CHART II

Experiment 3 (Ape "Herbert H"). In view of the fact that the respiratory catarrh of canine distemper can be produced in normal animals by subcutaneous inoculation of whole blood from an infected animal, we inoculated this normal chimpanzee subcutaneously with 8 cc. of bacteriologically sterile, citrated blood from a child with early whooping cough. On the fifth day this ape developed an upper respiratory catarrh exactly like that which followed the inoculation of unfiltered material. There was nasal discharge and fever (maximum temperature 101.4°F.) but no appreciable leucocytosis. The condition lasted six days. No cough developed (see Chart III).

Experiment 4 (Ape "Johann"). This normal ape was inoculated with the filtrate of fresh tracheal exudate from a child with early whooping cough. The exudate was promptly mixed with 25 cc. of yeast infusion broth and passed through a Berkefeld W filter. Five cubic centimeters of the filtrate were sprayed into

the animal's mouth and at the same time 8 cc. of blood from the same child were injected subcutaneously. After an incubation period of 7 days this ape developed a nasal discharge with fever (maximum 101.6°F.) but no appreciable leucocytosis. This lasted six days in all; no cough developed (see Chart IV).

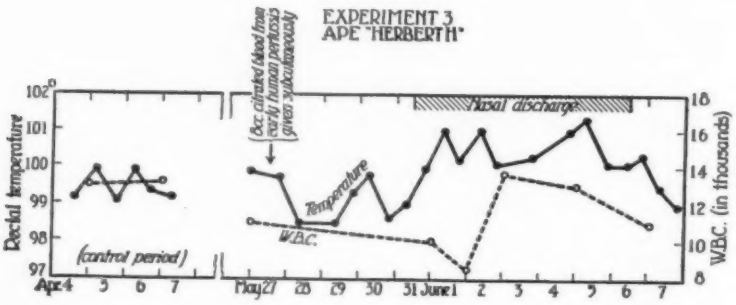

CHART III

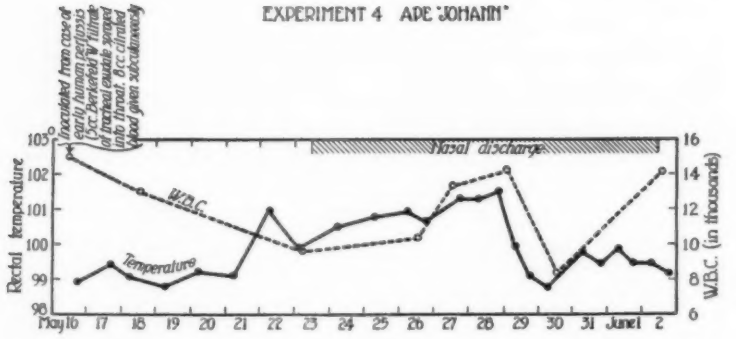
EXPERIMENT 4 APE "JOHANN"
Rectal temperature
W.B.C. (in thousands)
Nasal discharge
W.B.C.
Temperature
May 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 June 1 2

CHART IV

Experiment 5 (Ape "Darby"). This experiment was identical with the foregoing one with the exception that a Berkefeld V filter was substituted for a W filter and 3 cc. of the filtrate instead of 5 cc. were inoculated. On the sixth day after inoculation the animal developed a catarrhal condition with some fever lasting eight days (see Chart V).

Experiment 6 (Ape "Lucy"). This experiment was identical with the two preceding ones with the exception that a Seitz filter was used in place of a Berke-

feld candle, and only 4 cc. of citrated blood were given subcutaneously instead of 8 cc. On the seventh day a catarrhal condition developed similar to that in the preceding experiments; it lasted eight days (see Chart VI).

Experiment 7 (Ape "Becky"). In this experiment we attempted to transfer the catarrhal condition from one ape to a second, normal one. The throat

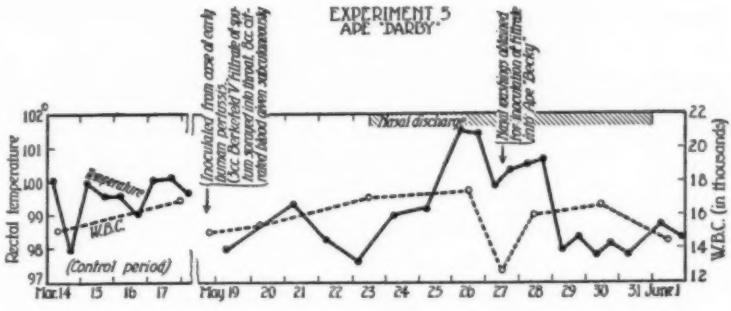
EXPERIMENT 5
APE "DARBY"
Nasal discharge
Temperature
W.B.C.
(Control period)
Rectal temperature
W.B.C. (in thousands)
Mar. 14 15 16 17 May 19 20 21 22 23 24 25 26 27 28 29 30 31 June 1

CHART V

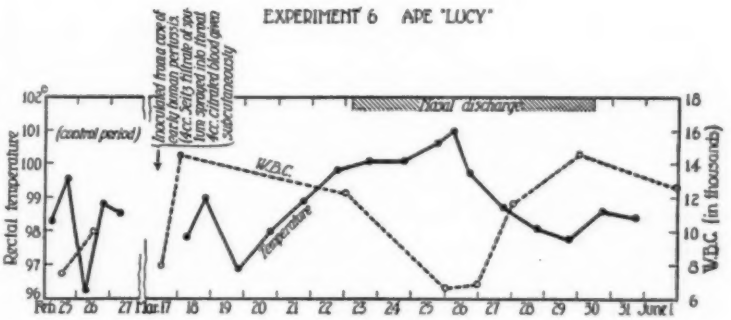
EXPERIMENT 6 APE "LUCY"
Nasal discharge
W.B.C.
Temperature
(control period)
Rectal temperature
W.B.C. (in thousands)
Feb. 25 26 27 Mar. 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 June 1

CHART VI

of "Becky," a normal ape, was sprayed with a Berkefeld W filtrate of the rhinopharyngeal washings obtained from the ape of Experiment 5 ("Darby") at the height (4th day) of the nasal discharge. The recipient, on the fourth day following the inoculation, developed a precisely similar catarrhal infection with slight nasal discharge, fever and no leucocytosis or cough. The catarrh persisted for a week and then disappeared (see Chart VII).

These experiments indicated that there was present in the blood and in the filtered exudate of each of the four early pertussis cases studied from this standpoint an agent capable of producing in apes an upper respiratory infection resembling the catarrhal stage of whooping cough, and that this catarrhal condition could be transferred from ape to ape by means of the filtered nasopharyngeal washings; and, further, that when Bordet-Gengou bacilli are present also, as in the case of the inoculation with unfiltered exudate, a paroxysmal cough with lymphocytosis may be produced in addition. Since the number of available chimpanzees was limited, we thought

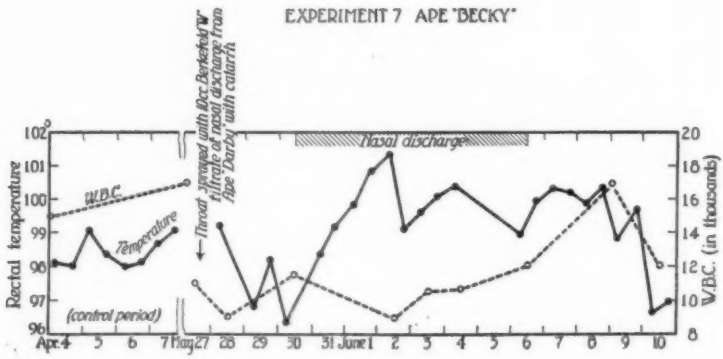

CHART VII

it best to determine next what effects could be produced by the inoculation with Bordet-Gengou bacilli alone. In the following three experiments normal apes were inoculated with pure cultures of recently isolated Bordet-Gengou bacilli.

Experiments 8 and 9 (Apes "Abe" and "Edith"). These two animals were inoculated with large doses of a third generation culture of Bordet-Gengou bacilli, recently isolated from a case of pertussis. In each case the bacilli from several agar slants were suspended in broth and gently instilled into the mouth of the animal. Neither ape developed any symptoms whatever. The complement fixation reaction was found to be negative four weeks after the original inoculation. Six weeks after the first inoculation these two animals were again inoculated with large doses of a third generation culture of the bacilli isolated from the ape in Experiment 2. This time each developed a transient nasal discharge, but neither

developed a cough and both remained well thereafter. Four weeks after the second inoculation both animals were found to have a positive complement fixation reaction.

Experiment 10 (Ape "Ape I"). A third normal animal was given a similar inoculation with a third generation culture of Bordet-Gengou bacilli recently isolated from a human case of pertussis. During the week following the inoculation some abscessed teeth were discovered and extracted. The subsequent removal of a sequestrum from the mandible was followed by a slight temperature

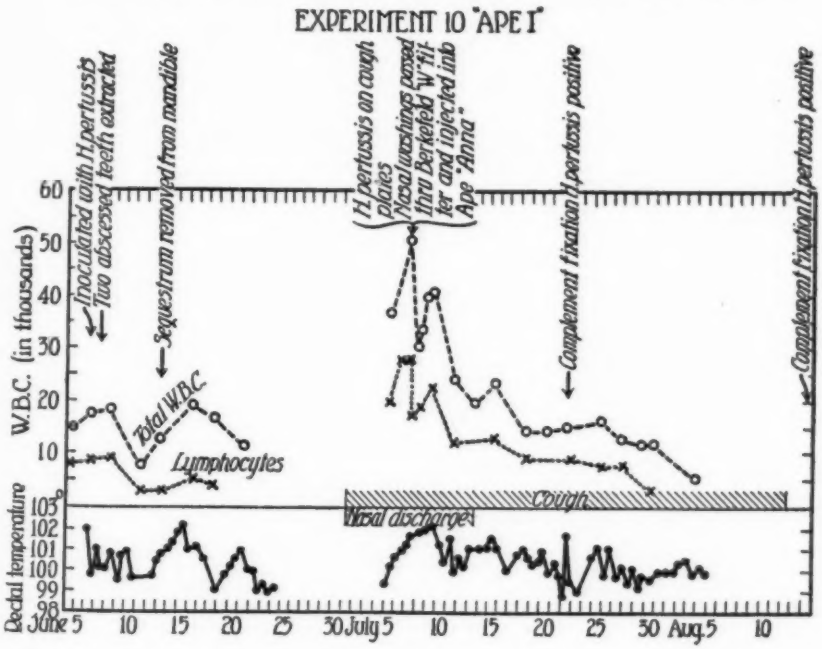

CHART VIII

reaction. However, the fever subsided promptly. The animal had no respiratory symptoms whatever during a period of 24 days following the inoculation, but then there appeared a nasal discharge accompanied by a cough which soon became paroxysmal, and a sharp rise in the lymphocytes. Bordet-Gengou bacilli were present in abundance on cough plates, and the complement fixation reaction was found to be positive on the 46th day following inoculation. The nasal discharge lasted 13 days. The paroxysmal cough and lymphocytosis lasted for 6 weeks, after which the animal was again normal and remained so (see Chart VIII).

In the following four experiments, pure cultures of Bordet-Gengou bacilli were given to apes that had recovered from the upper respiratory catarrh induced by bacteria-free filtrates or blood given subcutaneously. The interval between the first and the second inoculations was six weeks in two instances and ten weeks in two instances.

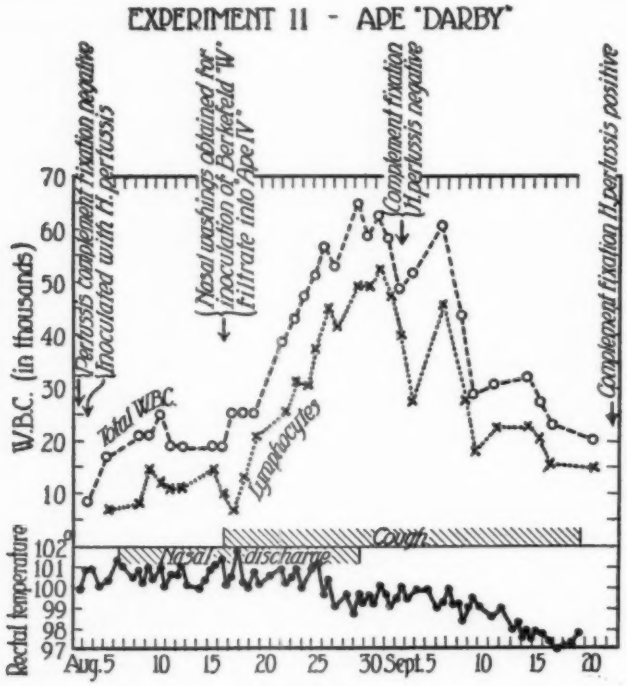

CHART IX

Experiment 11 (Ape "Darby"). This animal, 10 weeks after having been inoculated with filtered pertussis exudate (see Expt. 5), and two months after recovery from the catarrhal affection which resulted therefrom was inoculated by gently instilling into the mouth 5 cc. of a broth suspension of Bordet-Gengou from three agar slants of a third generation culture isolated from the ape in Experiment 2 ("Ape III"). H. pertussis complement fixation was negative. On the fourth day a purulent nasal discharge was noted. A cough somewhat paroxysmal in character appeared on the twelfth day, and the typical cough of pertussis was

noted on the nineteenth day after inoculation. A rise in lymphocytes began at about the fourteenth day, reaching its maximum (53,000) on the twenty-eighth day after inoculation. The paroxysmal cough and lymphocytosis lasted five weeks. Bordet-Gengou bacilli were recovered from the cough plates at this time. The complement fixation reaction was found to be positive on the 50th day (see Chart IX).

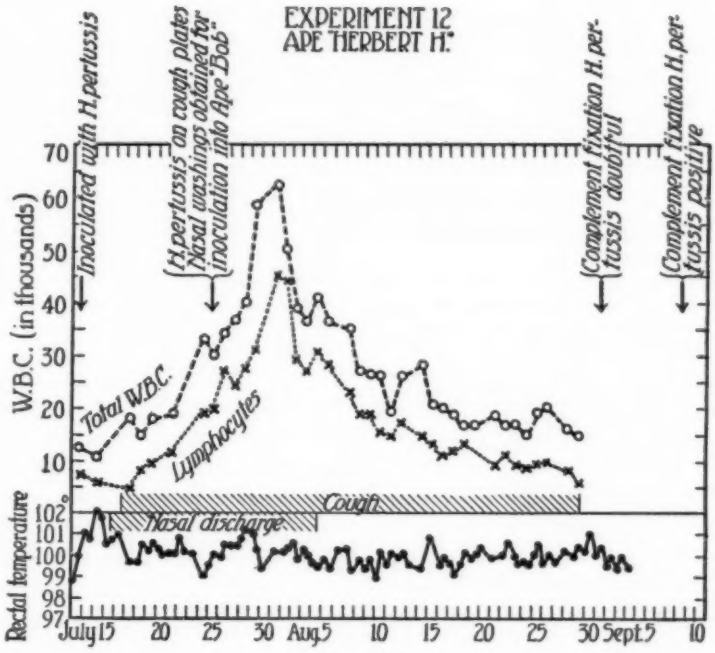

CHART X

Experiment 12 (Ape "Herbert H"). This animal was inoculated by instilling into the nose and mouth a broth suspension of the growth from 5 agar slants of a third generation culture of Bordet-Gengou bacilli isolated from the ape of Experiment 10 ("Ape I"). The inoculation was made 6 weeks after "Herbert H" had been inoculated with filtered pertussis exudate (see Expt. 3), and one month after recovery from the catarrhal affection which resulted therefrom. On the fourth day he developed rhinitis, and on the day following a paroxysmal cough was noted. This lasted six weeks. Lymphocytes rose sharply during the second and third weeks after inoculation, reaching their maximum (45,000) at the end

of the third week. The complement fixation reaction was found to be positive on the 59th day. Bordet-Gengou bacilli were recovered on cough plates (see Chart X).

Experiment 13 (Ape "Lucy"). This animal was inoculated intraorally and intranasally with 7 cc. of a heavy suspension of a third generation culture of

TABLE I

MATERIAL INOCULATED INTO APE	EXPERIMENT NUMBER	RESULT				
		Febrile coryza	Paroxysmal cough	Lymphocytosis	B-G bacilli recovered on cough plates	Complement fixation for B-G bacilli
Unfiltered exudate from human pertussis intra-orally	1	+	0	0	0	+
	2	+	+	+	+	+
Blood from human pertussis subcutaneously	3	+	0	0	0	0
Filtrate from human pertussis exudate intra-orally and blood from same patient subcutaneously	4	+	0	0	0	0
	5	+	0	0	0	0
	6	+	0	0	0	0
Filtrate of rhinopharyngeal washings of ape of experiment 5 during coryza, sprayed into throat	7	+	0	0	0	0
Border-Gengou bacilli intra-orally to normal apes	8	0/+	0	0	0	0/+
	9	0/+	0	0	0	0/+
	10	+	+	+	+	+
Bordet-Gengou bacilli intra-orally to apes which had recovered from coryza produced by filtrates (apes of experiments 4, 5, 6, 7)	11	+	+	+	+	+
	12	+	+	+	+	+
	13	0	0	0	0	0
	14	0	0	0	0	+
Filtrate of rhinopharyngeal washings of apes of experiments 10, 11, 12 at height of cough given intra-orally	15	0	0	0	0	0
	16	0	0	0	0	0
	17	0	0	0	0	0

Bordet-Gengou bacilli obtained from "Ape III" (Expt. 2), ten weeks after her first inoculation (see Expt. 6) and eight weeks after recovery from the upper respiratory catarrh. No symptoms whatever developed in this ape. The complement fixation was negative seven weeks after the inoculation with the bacilli.

Experiment 14 (Ape "Becky"). This ape, which had developed a respiratory catarrh from inoculation with filtrate from another ape (see Expt. 7), was given

intranasally and intra-orally a broth suspension of bacilli from 5 agar slants of a third generation culture of Bordet-Gengou bacilli recovered from "Ape I" (Expt. 10). The bacilli were inoculated six weeks after the filtrate inoculation. No symptoms of any sort resulted; the complement fixation reaction was negative on the eleventh day after this inoculation, but had become positive by the fifty-first day.

Thus, among seven apes that received in all nine inoculations of Bordet-Gengou bacilli, there developed in three instances a protracted paroxysmal cough, similar to that of the paroxysmal stage of whooping cough and accompanied by lymphocytosis. Filtrates (Berkefeld W) from the nasopharyngeal washings of these three apes during the height of the cough (apes from Experiments 10, 11 and 12) were sprayed into the throats of three normal apes (apes "Anna," "Ape IV" and "Bob"). None of these three animals developed any symptoms whatever.

DISCUSSION

Unfortunately, it was necessary to break up the available colony of chimpanzees at the close of the pertussis season during which the above experiments were carried out, and we have been unable to reestablish it. Since ferrets have been used successfully in the investigation of canine distemper, these animals were used by one of us (P. H. L.) in a number of inoculation experiments in which filtered and unfiltered exudates from cases of pertussis, as well as pure cultures of Bordet-Gengou bacilli, were used. The results were entirely negative. While we hope to be able to carry the work further with chimpanzees at a later time in the study of the nature and constancy of the filterable agent and of immunity to H. pertussis, there is no immediate prospect of reestablishing our colony, and it has seemed desirable to present the details of the experiments as they stand at present for, although they are obviously inconclusive in settling the question of the etiology of pertussis, certain deductions can nevertheless be drawn from them.

In the first place, Experiments 2, 10, 11 and 12 can properly be regarded as demonstrating that the chimpanzee is susceptible to whooping cough, for in all of these experiments every clinical and laboratory finding characteristic of the disease developed. In one of

these experiments (Expt. 2) a normal ape was inoculated with unfiltered tracheal exudate from a case of pertussis; in one instance (Expt. 10) a normal ape received a pure culture of Bordet-Gengou bacilli; and in two instances (Expts. 11 and 12) pure cultures of Bordet-Gengou bacilli were given to apes that had previously received filtrates of pertussis exudates. Following the inoculation, each of these four apes developed an upper respiratory catarrh, followed by a protracted cough which became paroxysmal. All developed a marked lymphocytosis. Bordet-Gengou bacilli were recovered in abundance on cough plates at the height of the cough some weeks after the inoculation; and the complement fixation reaction for these bacilli became positive.[3] The chimpanzee is, therefore, a suitable animal for the study of the disease.

In the second place, the experiments demonstrate that Bordet-Gengou bacilli, *acting alone*, in a normal animal are capable of producing typical whooping cough. This was clearly demonstrated in Experiment 10, and Experiments 11 and 12 may reasonably be regarded in the same light for, although these latter two apes had previously been inoculated with sterile filtrates of pertussis exudate, $1\frac{1}{2}$ and $2\frac{1}{2}$ months respectively had elapsed between the filtrate inoculation and the inoculation of the pure culture of Bordet-Gengou bacilli which led to the development of the signs, symptoms, and laboratory findings typical of whooping cough.

That we have reproduced in the chimpanzee all of the characteristic clinical and laboratory features of whooping cough by the inoculation of pure cultures of Bordet-Gengou bacilli alone there can be no doubt. This fact, which we reported in 1932 (19), has since been confirmed by Shibley (14); and MacDonald and MacDonald (15) have reported the production of the essential features of the disease in two children by instilling Bordet-Gengou bacilli into the nose and throat. Since the disease *pertussis* was not produced in the experi-

[3] It is interesting to note that, in addition to these four apes that developed positive complement fixation in association with typical whooping cough, there were four others (Experiments 1, 8, 9 and 14) in which positive complement fixation developed following inoculation in the complete absence of a cough. Three of these apes had developed coryza only, and one had no symptoms of any sort.

ments in which filtrates of the tracheal exudate from active human cases were used, the only positive conclusion that can be drawn from our study is that the Bordet-Gengou bacillus, unaided by any other agent, is capable of causing the disease. Unfortunately, the filtrate experiments are too incomplete to permit any conclusion regarding the nature of the catarrh-inciting agent, the constancy of its presence in early cases of pertussis, or its relation to the disease; and until further work is done we cannot with assurance reckon upon any agent other than the Bordet-Gengou bacillus as playing a rôle in the etiology of whooping cough. On the other hand, it is our feeling that until further work is done we cannot with final assurance regard the Bordet-Gengou bacillus as the sole cause of the natural disease. In our experiments very large doses of bacilli were inoculated; and even in the face of those large doses, which were tremendously in excess of any to which the human being is ever exposed in natural infection, only three out of nine inoculations resulted in the production of the disease. Since the apes in Experiments 11 and 13 were inoculated with the same generation of the same culture, and those in Experiments 12 and 14 with the same generation of another culture, and since the animals of Experiments 11 and 12 developed pertussis while those of Experiments 13 and 14 did not, one can hardly explain the variability in reaction on the basis of differences in the virulence of the bacilli used. Either the human being is far more susceptible to the bacillus than is the chimpanzee, or else a concomitant virus may serve to enhance susceptibility in natural infection. It is of some interest that in each of the experiments in which unfiltered exudate from cases of pertussis was inoculated (Experiments 1 and 2) the complement fixation reaction for Bordet-Gengou bacilli became positive, whereas in three of the experiments in which enormous numbers of bacilli were inoculated (Experiment 13 and first inoculations in Experiments 8 and 9) positive complement fixation failed to develop. These experiments are, however, too few in number to be regarded as significant.

Although we have produced all of the characteristics of whooping cough by the inoculation of pure cultures of Bordet-Gengou bacilli, the conclusion that this bacillus is the sole etiological agent of the natural disease is disturbed by the fact that in each of the four in-

stances in which normal apes were inoculated with sterile filtrates of tracheal exudate and sterile blood from cases of early whooping cough (Experiments 3, 4, 5 and 6) an upper respiratory affection closely resembling the catarrhal stage of whooping cough developed; and in the one instance in which we attempted to transfer this condition by filtrate from one ape to a second normal one, the attempt was successful (Experiment 7). The nature and significance of the agent responsible for this catarrhal condition remains undetermined. Our limited data certainly do not permit the conclusion that it is a specific filterable virus that acts to increase susceptibility to infection with the Bordet-Gengou bacillus, analogous to the action of the filterable virus of swine influenza or canine distemper. Indeed, we are unable to state with certainty that this agent is not the virus of the common cold. It is well known that the catarrhal stage of pertussis closely resembles the common cold, and the symptoms of the catarrhal condition produced by the pertussis filtrates in our apes presented no differential feature; however, the incubation period (4 to 8 days) was distinctly longer than that which one of us (P. H. L.) had found in a previous year to be the rule in these same apes when inoculated with filtrates from common colds (average of 2 days). It may be remarked that the incubation period of whooping cough in man, if measured by the onset of the catarrhal symptoms, is somewhat longer than that of the common cold. The presence of the filterable agent in the blood, as shown in Experiment 3, is a feature that has not hitherto been described in the case of the common cold virus, and it will be desirable to determine whether the virus of the common cold can be demonstrated in the circulating blood. It is also necessary to determine in a larger series of cases whether the filterable agent found in the present cases of pertussis is demonstrable with regularity in the early stage of the disease and, if so, whether or not it acts to enhance susceptibility to the Bordet-Gengou bacillus. Until these questions are answered we can hardly speak with satisfying finality regarding the etiology of whooping cough.

It must be remembered that a condition closely resembling canine distemper can be produced in dogs by pure cultures of Bacterium bronchisepticum, and that with Bacterium suipestifer a condition closely resembling hog cholera can be produced in swine. These bacteria were, therefore, long regarded as the sole etiological agents

of those diseases, until it was learned that in each case, in the natural disease, the micro-organism in question is associated with a specific filterable virus which is responsible for the high degree of contagiousness and for the durable immunity conferred by an attack. The fact that we have reproduced the essential characteristics of pertussis by inoculating apes with the Bordet-Gengou bacillus is, therefore, insufficient evidence that this bacillus is the sole etiological agent in the natural disease. The innumerable unsuccessful or equivocal attempts to immunize satisfactorily against pertussis by means of vaccines made from Bordet-Gengou bacilli remind one of the many similarly unsuccessful attempts to immunize dogs satisfactorily against distemper with vaccines prepared from Bact. bronchisepticum. It is now known that effective immunity in this latter disease can be produced only by vaccination with the filterable virus. The recent favorable reports by Sauer (17) relating to successful immunization against pertussis with a Bordet-Gengou bacillus vaccine will, if substantiated by general experience, serve to remove one of the major objections to the view that the Bordet-Gengou bacillus is the sole cause of pertussis. Unfortunately, we were unable to maintain our chimpanzee colony long enough to carry out satisfactory immunity tests.

SUMMARY

1. A condition similar in all respects to whooping cough, and characterized by coryza followed by a protracted, paroxysmal cough typical of that of pertussis, associated with lymphocytosis and the development of positive complement fixation toward the Bordet-Gengou bacillus, has been produced in the chimpanzee by oral inoculation with unfiltered tracheal exudate from human pertussis. Bordet-Gengou bacilli were recovered on cough plates at the height of the cough.

2. A precisely similar condition has been produced in the chimpanzee by oral inoculation with pure cultures of Bordet-Gengou bacilli. It is therefore clear that the characteristic clinical features of pertussis can be produced in apes by these bacilli acting alone.

3. The inoculation of apes with bacteriologically sterile blood and filtered respiratory secretions obtained from each of four cases of pertussis early in the disease was followed by the appearance of a

upper respiratory catarrh without cough. In the one instance in which an attempt was made to transfer the agent from one ape to another by means of a bacteriologically sterile filtrate of the nasopharyngeal secretions, the attempt was successful.

4. The nature of this filterable agent is discussed. Its relation to pertussis is undetermined. At present one can say only that the Bordet-Gengou bacillus, acting alone, is capable of producing the characteristic clinical manifestations of whooping cough in the ape.

REFERENCES

(1) RICH: *Bull. Johns Hopkins Hosp.*, 1932, **51**, 346.
(2) FRAENKEL: *Münch. Med. Woch.*, 1908, **55**, 1683.
KLIMENKO: *Cent. f. Bakt.*, 1909, **48**, 64.
INABA: *Ztschr. f. Kinderh.*, 1912, **4**, 252.
(3) SAUER AND HAMBRECHT: *Am. J. Dis. Child.*, 1929, **37**, 732.
(4) MALLORY, HORNER AND HENDERSON: *J. Med. Res.*, 1912–13, **27**, 391.
ARNHEIM: *Arch. f. Kinderh.*, 1909, **1**, 296.
POLETT: *Cent. f. Bakt.*, 1909, **69**, 23.
BACHMANN AND BERGHARD: *Ztschr. f. Kinderh.*, 1925, **39**, 465.
MELFI: *Semana Med.*, 1923, **30**, 1125.
WOLLSTEIN: *J. Exp. Med.*, 1909, **11**, 41.
(5) BLAKE AND CECIL: *Ibid.*, 1920, **32**, 691, 719.
(6) NIEMANN: *Berl. klin. Woch.*, 1919, **56**, 777.
HOLT AND HOWLAND: Diseases of Infancy and Childhood, 9th ed., D. Appleton and Co., New York, 1926, p. 945.
HOLT: *Arch. Ped.*, 1914, **31**, 724.
KUCZYNSKI AND WOLFF: *Ergebn. d. allg. Path.*, 1921, XIX_2, 977.
(7) BROWN: *Bull. Johns Hopkins Hosp.*, 1926, **38**, 147
(8) JOCHMANN AND HEGLER: Lehrbch. d. Infektionskrankh., Berlin, 1924, p. 344.
LAUCHE: Henke-Lubarsch Hdbch. d. spez. path. Anat. u. Histol. Berlin, 1928, III_1, 794.
(9) SHOPE: *J. Exp. Med.*, 1931, **54**, 373.
MCCORDOCK AND MUCKENFUSS: *Am. Jour. Path.*, 1933, **9**, 221.
(10) MACCALLUM: *Johns Hopkins Hosp. Reports*, 1921, **20**, 149.
(11) FEYRTER: *Frankf. Zeit.*, 1927, **35**, 213.
(12) CULOTTA, HARVEY AND GORDON: *Jour. Ped.*, 1935, **6**, 743.
(13) ARNHEIM: *Berl. klin. Woch.*, 1903, **40**, 665.
(14) SHIBLEY: *Proc. Soc. Exp. Biol. and Med.*, 1934, **31**, 576.
(15) MACDONALD AND MACDONALD: *J. Inf. Dis.*, 1933, **53**, 328.
(16) FORD: *Am. J. Dis. Child.*, 1929, **37**, 1046.
(17) SAUER: *J. A. M. A.*, 1933, **101**, 1449.
(18) FARBER AND WOLBACH: *Am. Jour. Path.*, 1932, **8**, 123.
(19) RICH, LONG, BROWN, BLISS AND HOLT: *Science*, 1932, **76**, 330.
(20) MCCORDOCK: *Proc. Soc. Exp. Biol. and Med.*, 1932, **29**, 1288.

THE DIAGNOSIS OF OBSCURE FEVER

II. The Diagnosis of Unexplained High Fever

LOUIS HAMMAN and CHARLES W. WAINWRIGHT

From the Department of Medicine, Johns Hopkins University

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As we have said, it is convenient for purposes of exposition to consider separately the diagnosis of unexplained low-grade fever and unexplained high fever. Nevertheless, it must be apparent that the division, though practically useful, is artificial. Diseases which frequently cause low-grade fever occasionally are manifested by high fever and those which usually cause high fever may less often be accompanied by low fever. Therefore, the diseases which have already been described as often being accompanied by low fever must now again be taken into account when describing the causes of high fever. For instance, Malta fever is a frequent cause of obscure low-grade fever but at times causes high fever; tuberculosis, the commonest cause of unexplained high fever, less often produces a long-continued, unexplained low fever; the growth and spread of malignant tumors is often accompanied by high fever but hardly less frequently by low-grade fever. These well-known facts are recalled and stressed to obviate the necessity of repetition.

In discussing the diagnosis of high fever of obscure origin we may classify the diseases most often responsible as follows:

1. Septicemia.
2. Localized septic infections and abscesses.
3. Specific infections.
4. Diseases of the blood-forming organs.
5. Malignant tumors.

In our series of ninety cases of obscure fever there are fifty-four with high fever. No satisfactory diagnosis was ever reached in ten of these. In the remaining forty-four a diagnosis was finally made from the development of characteristic symptoms, at operation or

at autopsy. In thirty-four of the cases the diagnosis was established beyond any reasonable doubt; in the remaining ten the diagnosis rested solely upon clinical evidence which was fairly convincing, yet might be questioned. The diagnoses made upon the forty-four cases were as follows:

1. Septicemia:	
Gonococcus	2
2. Localized septic infections:	
Perirenal abscess	1
Liver abscess	1
Perisplenic abscess	1
3. Specific Infections:	
Syphilis	10
Tuberculosis	9
Malta fever	4
Tularemia	1
Typhoid	1
Malaria	1
Amaebiasis	1
4. Diseases of the blood-forming organs:	
Hodgkin's disease	4
5. Malignant tumors:	
Hypernephroma	5
Carcinoma of lung	1
Carcinoma of liver	1
Sarcoma of spleen	1

1. SEPTICEMIA

Invasion of the blood stream with the streptococcus or the staphylococcus seldom baffles diagnosis. Blood cultures are now almost universally made on all patients with fever, and when this method of investigation is used persistently, cases of streptococcal or staphylococcal septicemia rarely escape detection. Twenty-five or thirty years ago subacute bacterial endocarditis due to Streptococcus viridans was a common cause of unexplained fever. In those days blood cultures were made only at large medical centers and the characteristic clinical features of the disease were recognized only by experienced consultants. At the present time every practising physician is thoroughly familiar with the distinctive clinical picture, and blood cultures nearly always reveal the infecting organism so that the diagnosis is seldom missed. If a patient with fever has the accom-

panying symptoms which plainly indicate the presence of subacute bacterial endocarditis but repeated blood cultures remain sterile, then we strongly suspect that the infection is due to an organism other than Streptococcus viridans.

Gonococcal septicemia is more often overlooked than any other bacterial form of blood stream invasion. This is a matter worthy of emphasis and of very careful clinical examination. All are familiar with the classical form of gonococcal septicemia producing high fever, a decided leukocytosis, often involving the valves of the right side of the heart and running a rapidly fatal course over a period of two or three weeks. However, it is seldom taken into account that the gonococcus may cause a relatively benign, long-continued infection marked only by a relatively low fever, a slight or absent leukocytosis, and involve preferably the aortic valves. This disease is often misinterpreted, since the gonococcus is difficult to grow and repeated blood cultures may remain sterile. There are two of these cases in our series and on account of the importance of the condition the facts concerning one are reported.

Case No. 4. M. S., Unit history No. 55348. A young, colored woman, 29 years of age, entered the Johns Hopkins Hospital May 8, 1934, complaining of shortness of breath and swelling of the ankles. She had been well until about ten months before when she had begun to have shortness of breath on exertion. This gradually had grown more pronounced and the symptoms had been further aggravated by a severe cold which had come on a month or two later. She had had a good deal of cough and had raised a large amount of yellowish sputum which never had been bloody. The cough had persisted up to the time of her admission to the hospital. Three weeks before entering the hospital swelling of the ankles, legs and abdomen gradually had come on. This had been worse in the evening than when she got up in the morning. One week before admission she had begun to have night sweats which had recurred nightly up to the time of her admission. There had been also some pain about the heart though not particularly severe Her chief complaints were shortness of breath and swelling of the legs.

In 1920 the patient had been operated upon for pus in the abdomen which was said to have come on after a fall. In 1926 she had had pain in one of the ankles which had lasted about a week but had not been sufficiently severe to keep her in bed.

Examination. Temperature 101°; pulse, 88; respirations, 24; blood pressure, systolic 164, diastolic 68.

The patient was a large, well nourished, colored woman lying comfortably in bed with only slight shortness of breath. She was unusually amiable and good

natured. The eyes were normally prominent; the eye movements well performed. The pupils were equal, the right somewhat irregular; both reacted sluggishly to light but actively on accommodation. The eyegrounds showed no noteworthy abnormality. The teeth were in fairly good condition. The pharynx showed nothing remarkable except that the mucous membranes were rather pale. One or two palpable glands in the neck, otherwise no enlargement of the superficial lymph nodes. The thyroid was not enlarged. The chest well formed and symmetrical, movements equal on the two sides. There was a little dulness at the bases of both lungs and many coarse râles were heard over both lower lobes. There was a very wide and intense pulsation over the whole heart. No definitely localized apex beat. The area of cardiac dulness measured 3.5 cm. to the right and 13 to the left of the midline. All over the heart was heard a loud systolic and a loud diastolic murmur. The first sound at the apex was diminished in intensity. The diastolic murmur was particularly loud down the left border of the sternum. The pulse was regular, equal at the two wrists, very collapsing in quality. The abdomen was held rigidly; no tenderness; no masses could be felt. The liver edge was 4 cm. below the costal margin. There was a little shifting dulness in the flanks. The spleen was not felt. The pelvic examination showed the presence of a large mass apparently connected with the fundus of the uterus. This was thought to be a fibromyoma. The rectal examination was negative. The neuromuscular examination showed no abnormality. There was well marked edema of the legs and thighs.

Course in the hospital. After admission to the hospital the patient's general condition improved and the edema rapidly disappeared. She lost thirty-six and a half pounds in weight. Late in June her voice was hoarse and the laryngologist reported paralysis of the left vocal cord. No important changes occurred in the physical signs over the heart. However, there was a good deal of discussion about the interpretation of these signs. Some felt that there was definite evidence of mitral disease; others that the mitral signs were relative to the aortic insufficiency. At first the spleen was not felt, but later a number of observers said that the spleen was easily felt and one affirmed that it was large and firm. The point of greatest importance in the course of events was the fact that the patient constantly had fever for which no satisfactory explanation was found. On admission to the hospital the temperature varied between 99° and 100.6° and it continued at this level sometimes going to 101° and occasionally even to 102°. Some suggested that the enlargement of the liver and spleen might be associated with the syphilitic infection. She was very thoroughly treated with iodides but this had no effect upon the fever. No embolic phenomena were ever noted and the fingers were not clubbed. The possibility of bacterial endocarditis was constantly held in mind but the blood cultures were consistently negative. After the patient had been in the hospital for nearly four months she was discharged somewhat improved.

Laboratory Examinations. Blood count: May 8, 1934: Hbg. 64%; Red Blood Cells 3,740,000; White Blood Cells 6,200. Differential count essentially normal. July 21: Red Blood Cells 3,120,000; White Blood Cells 8,600.

Wassermann reaction on the blood serum strongly positive.

Blood culture: May 21: No growth. June 2: No growth. June 25: No growth. July 9: No growth. July 13: No growth.

Urine culture: May 21: No growth. June 8: No growth. July 27: No growth.

Agglutination tests for Bacillus melitensis negative.

Urine: Specific gravity varied from 1.007 to 1.014. There was always a large amount of albumin varying from a trace to 3 gms. per liter. Sediment contained a small number of pus cells, only occasionally a few red blood corpuscles and now and again a few casts.

Phthalein test of renal function: June 5: 35% in two hours. July 13: 42% in two hours.

Spinal puncture: 12 cc. clear, colorless fluid. Two cells. Pandy negative. Wassermann negative. Colloidal mastic test negative.

Liver function tests, June 4: Levulose tolerance test: Fasting, 80 mg.%; ½ hour, 95 mg.%; 1 hour, 110 mg.%; 1½ hour, 85 mg.%; 2 hours, 85 mg.%. Bromsulphalein test: No retention after thirty minutes.

Roentgenograms: May 14: Chest: Cardiac shadow markedly enlarged; aorta dilated; secondary changes in both lungs probably with fluid at right base. Tele.: M.R. 4.5, M.L. 11.7, A. 6.3, T. 26.1. June 21: Fluoroscopic examination: No evidence of an abdominal aneurysm.

Electrocardiograms: May 9: Normal sinus rhythm. The electrical axis lies at plus 69 degrees which is the quadrant of the normal axis. P I is small and practically isoelectric. T. waves are indistinct in all leads. QRS complexes in lead I are thickened. May 14: Normal sinus rhythm. The electrical axis in this record lies at plus 99 degrees, which is in the quadrant of right axis deviation. T I and II are iso-electric. T III biphasic.

Course after leaving hospital. After leaving the hospital the patient reported to The Syphilis Clinic where she received one injection of bismuth. On September 6 the note is made "feeling fine"; on September 17 "looks weak, slightly dyspneic, no edema." On September 18 the patient was brought to the hospital as an emergency but she was dead upon arrival. Precisely what had happened during the last few days of life is not known.

Anatomical Diagnosis. Bacterial endocarditis of aortic valves (gonococcus). Cardiac hypertrophy. Chronic passive congestion of viscera. Infarcts of spleen and kidney. Hyperplasia of bone-marrow. Chronic cystitis, pyelitis and pyelonephritis. Early carcinoma body of pancreas. Hemorrhage in pancreas. Old adhesions about both lungs, liver, spleen, ovaries and tubes. Multiple myomata uteri.

Other forms of septicemia may for a time escape detection. The influenza bacillus may localize upon the heart valves and produce the typical clinical symptoms of subacute bacterial endocarditis. The organism is nearly always identified in blood cultures.

2. LOCALIZED SEPTIC INFECTIONS

The localization of areas of septic infection or abscesses often presents a difficulty in diagnosis. The matter is so well known that it deserves no extended comment. Even when irregular fever and a high leukocytosis tell us that an abscess is likely to be present, for a long time we may be unable to find it. Older physicians will recall, for instance, what a boon is the roentgen ray in discovering pockets of interlobar empyema. Three of these cases particularly interested us.

Case No. 5. E. S. W. History No. 17,759. A young white woman, 24 years of age, entered the Union Memorial Hospital complaining of fever. Three weeks before, after slight exposure, she had become chilly and feverish. A little later pain in the right side had come on, made worse by deep breathing. There was a little tenderness over the liver and her physician thought she was lightly jaundiced. The pain in the right side had soon subsided but ten days before admission to the hospital she had begun to have pain about the left hip and in the lumbar region. Constantly during these three weeks she had had irregular fever and had become weak and pale. The patient was sparely nourished and pallor was conspicuous. The abdomen was rather tense but there was no localized tenderness, no muscle spasm and no mass could be felt. The blood count demonstrated a decided anemia and the leukocyte count varied from 22,000 to 28,000. The temperature was irregularly elevated, in the morning only a little above normal, in the evening rising to a point between 102° and 103.6°. Later it was learned that an abortion had been performed upon the patient a few days before the onset of the illness. In spite of the report of the gynecological examination which stated that the pelvic organs were quite normal it was assumed that a retroperitoneal abscess had formed as a result of pelvic infection. While the patient was under observation tenderness and fulness developed in the left flank but no definite mass could be outlined. Two weeks after admission to the hospital the patient was operated upon. An incision in the left lumbar region opened directly into a large perirenal abscess. The abscess was drained and the patient speedily recovered.

Case No. 6. M. K. Unit History No. 27614. A colored laborer, 36 years of age, entered the Johns Hopkins Hospital complaining of fever, general malaise and abdominal pain and tenderness. Shortly after admission an exploratory operation was performed under the assumption that the patient had tuberculous peritonitis or an abscess about the liver or kidney. No evidence of any disease of the abdominal cavity was discovered. The patient continued to have high fever, chills and a pronounced leukocytosis. He became more and more deeply intoxicated and died in coma six weeks after the onset of the illness. Autopsy revealed an abscess in the right lobe of the liver from which the gonococcus was recovered. This case has been more fully reported by Carter and Baker (1).

Case No. 7. G. A. F. History No. 37974. A white laborer, 38 years of age, entered the hospital complaining of weakness and bulging of the ribs on the left side. Three months before he had noticed increasing prominence of the ribs and after meals pain in the left upper quadrant of the abdomen. His appetite had failed and progressively he had lost weight and strength. For a number of weeks he had had fever and an occasional chill. The patient was pale and weak and had evidently lost much weight. The left costal margin was prominent and the left diaphragm high. Below the costal margin a firm mass was felt. The blood count revealed grave anemia and a decided leukocytosis. The nature of the mass below the left costal margin was not definitely decided upon. Some thought it to be a kidney tumor, others an enlarged spleen. There was much discussion about the possibility of the patient having Hodgkin's disease. The Wassermann test was strongly positive. Fever and leukocytosis persisted, the patient grew steadily weaker and died five weeks after entering the hospital. The postmortem examination disclosed a ruptured ulcer of the stomach and a large abscess about the spleen.

3. SPECIFIC INFECTIONS

Any of the specific infections may occur at times with atypical symptoms and for many weeks be masked as unexplained fever. We recall two especially interesting cases of meningococcus septicemia without meningeal symptoms reported from the Johns Hopkins Hospital in 1921 by Morgan (2). We have already commented upon the importance of Malta fever and rheumatism as causes of obscure fever.

Syphilis. Ten instances of syphilitic fever are included in our series of ninety cases. The number is astonishing and must represent a distorted proportion. The cause of this distortion is not altogether clear. No doubt it is at least partly due to the fact that these cases always make a profound impression upon the observers, owing to the dramatic cure which follows the administration of iodides, and therefore are remembered; partly, because five of them were reported upon in 1923 by Thayer (3), two more in 1933 by Futcher (4), and these seven are included in our ten cases. In former years cases of syphilitic fever could be detected only by the therapeutic test and today, in spite of the almost universal use of the Wassermann reaction, the result of treatment remains the sole criterion of the validity of the diagnosis. It is safe to conclude that fever which resists the taking of iodides for a week is not syphilitic fever. A characteristic instance of this puzzling condition was the following:

Case No. 8. I. C. B. Unit History No. 19307. A colored woman 26 years of age, was admitted to the Johns Hopkins Hospital on March 27, 1932, complaining of weakness, sweats, cough, expectoration and pain in the lower right side of the chest. Her husband had died of syphilitic heart disease in a Ward of the Johns Hopkins Hospital in 1931. The patient had been married to him for nine years and from 1922 to 1925 had had four healthy children born at term. In 1928 and 1929 there had occurred two still-births. In 1929 her Wassermann reaction had been found to be positive. She had been treated in the Out-patient Department, and in March 1930 had given birth to a healthy child.

The examination revealed no abnormality excepting as regarded the chest. At first a friction rub was heard at the base of the right lung and later appeared the signs of fluid in the right pleural space. Paracentesis yielded on one occasion 40 cc., on another 10 cc. of hemorrhagic exudate. No tubercle bacilli were demonstrated by microscopical study or by guinea-pig inoculation. During her stay of two weeks in the hospital the temperature ranged from 99° to 102°F.

The patient was then transferred to a tuberculosis sanatorium where she remained only three weeks. A diagnosis was made of latent syphilis and acute pleurisy of undetermined origin.

She entered the hospital again on June 21, 1932, stating that three weeks before she had had a profuse uterine hemorrhage, and that two weeks before there had been an exacerbation of her previous symptoms, namely, fever, chills, sweats, nausea and vomiting, and cough with mucoid expectoration.

The patient now was very ill. The temperature was 107°. Again the only noteworthy findings on physical examination were those about the chest. Over the left posterior axillary region and over the left base the percussion note was impaired, the breath sounds were distant and crepitant râles were heard. The red blood cells numbered 2,110,000, the leukocytes 18,600; Hemoglobin 55%. The differential count included 88% polymorphonuclear cells. A roentgenogram of the chest showed that the pleurisy present at the right base in April had entirely disappeared, and that now there was infiltration of the left lower lobe of the lung. This condition progressed so that on June 27 the roentgenogram disclosed pneumonic consolidation at the left base. The patient continued to be very ill, the temperature on June 27th reaching 108.2°. There was abundant sputum, 100 to 200 cc. a day; tubercle bacilli were never found; cultures yielded hemolytic Staphylococcus aureus. There were a few spirochetes and fusiform bacilli in the stained smears. Repeated blood cultures were negative. The Wassermann reaction on the blood serum was positive. In July roentgenograms suggested that cavitation had begun in the lower lobe of the left lung. The temperature had continued to be high, reaching 103° each day. On July 8, 1932, the administration of potassium iodide was begun; at first, through an error, only 0.2 gm. was given three times a day, later the dose was increased to 0.3 gm. three times a day. In spite of the small amount of potassium iodide which was given, three days after it had been begun, on July 11, there was an abrupt fall of the temperature which reached normal seven days later. The pulmonary condition rapidly cleared and

on August 14 only areas of partial consolidation in the left lower lobe and thickening of the pleura could be demonstrated. The patient was discharged from the hospital September 29, 1932, at which time the Wassermann reaction had become negative.

When the patient reported three months later she had gained 20 pounds in weight, the cough had entirely disappeared, and the roentgenogram of the chest showed only moderate fibrosis of the left lower lobe.

Tuberculosis. Of all the chronic infections tuberculosis more often than any other is disguised as obscure fever. In our series we include nine of these cases. We shall report in detail only one, but we recall very vividly the old colored man who came into the hospital complaining of vague pain about the heart, shortness of breath and prostration, and who on examination betrayed severe generalized arteriosclerosis, enlargement of the heart, mild symptoms of congestive heart failure and constantly a little fever. It was assumed that he had arteriosclerotic heart disease. One day he complained more bitterly than before of precordial pain, and a transient friction rub was heard over the heart which seemed to justify the diagnosis of coronary occlusion. The postmortem examination revealed tuberculous pericarditis. Also the forty-two year old soldier followed at the Veterans Bureau Facility, Washington, D. C., who was badly crippled by infectious arthritis, which had become quiescent, and who ran a high irregular fever with frequent chills for about four months before he died. In addition to the arthritic manifestations he showed loss of weight and profound anemia of an aplastic type. The examination otherwise was entirely negative except that on a few occasions the spleen was indefinitely felt. The general opinion favored a blood stream infection, although repeated blood cultures remained sterile. At autopsy all were surprised to find extensive tuberculosis of spleen, liver and peritoneum. The case we have selected as an illustration is the following:

Case No. 9. D. L., Unit History No. 48565. A colored laborer, 62 years of age, entered the hospital on April 3, 1933, complaining of swelling of the abdomen. He always had been remarkably well. At fifteen years of age he had had an illness characterized by general aching which he called rheumatism. However, there had been no definite joint manifestations. At twenty-two years of age he had had an attack of pneumonia. Two years before coming into the hospital he had noticed some shortness of breath on exertion, but this was by no means severe and

had not interfered with his work. One year before his final illness he had become yellow and had had double vision which came and went for a period. The illness which brought him to the hospital had begun four weeks before when he noticed that his abdomen was swollen. The swelling had increased and a little later both legs had become somewhat swollen. The dyspnea which had been present to a slight degree for two years had now become much more pronounced. However, in spite of these symptoms he had continued at his work until three or four days before he was admitted. During this period of a month he had cough especially at night and he occasionally brought up a little sputum which never was bloody. For two weeks before he had had hoarseness and for one week the urine had been very dark in color.

Examination. Temperature 99°, pulse, 134, respirations, 38; blood pressure, systolic 156, diastolic 110.

The patient was a sparely nourished old colored man propped up in bed with marked dyspnea. Apparently he had lost some weight. He was genial, co-operative and mentally perfectly clear. The mucous membranes and the nails were a little cyanotic. The veins in the neck were somewhat engorged. There was edema over the sacrum and over both shins. He had a dry cough with little or no expectoration. Breathing was for the most part regular but occasionally it was Cheyne-Stokes in type. The eyes were normally prominent, the eye-slits narrow, the lids a little puffy. The extra-ocular movements were normal. The pupils were equal, the right a little irregular; they both reacted to light and on accommodation. There was a well-marked arcus senilis. There was slight clouding of both lenses; the discs were clear; the retinal arteries were tortuous, had a prominent central stripe and indented the veins somewhat where they passed over them. The teeth were in very bad condition; they consisted mostly of decayed stumps and there was an extreme degree of gingivitis and pyorrhea. The throat showed nothing remarkable. Many of the superficial lymph nodes, including the epitrochlears, were palpable but none were particularly enlarged. The thyroid was normal in size. The trachea was in the midline. There was no tracheal tug. The chest was rounded, the anteroposterior diameter increased. The manubrium and upper portion of the sternum were prominent. Expansion of the chest was everywhere limited. The lungs showed the characteristic signs of a moderate degree of emphysema and there were moist râles at the bases of both lungs. The apex beat of the heart was located in the fourth interspace, 8.5 cm. from the midline. Dulness measured 5 cm. to the right and 9.5 cm. to the left of the midline. There was some dulness over the manubrium. The heart sounds were clear, they were muffled and of poor quality. There was protodiastolic gallop. The second pulmonic sound was louder than the second aortic. The pulse was regular, the peripheral vessels were tortuous and sclerosed. The abdomen was symmetrically prominent. The walls were soft. There was slight tenderness in the epigastrium. There was a small amount of free fluid in the peritoneal cavity. The liver edge extended to a point three fingerbreadths below the costal margin. The spleen was not felt. The genitalia showed nothing abnormal. The rectal examination

was negative. The prostate was small and firm. The neurological examination was entirely negative.

Course in the hospital. (First Admission.) The patient was at once put upon the usual treatment for myocardial insufficiency and there was prompt improvement in his condition. The following day he was quite comfortable and during the succeeding five days he lost twenty-six pounds in weight, edema vanished and fluid could no longer be demonstrated in the peritoneal cavity. At the end of a week he was perfectly comfortable and all the signs of myocardial insufficiency which had been present at the time he entered the hospital had completely disappeared. During the first ten days in the hospital the temperature was at the normal level. Only occasionally did it go as high as 99°. On the eleventh day it rose to 99.4°, the following day to 99.6°, and then to 101°. From April 17 to May 12 there was a low grade fever varying from 99° to 101°; from May 12 to June 1 it was higher, varying irregularly from 99° to 103.8°. From June 1 to 13 the temperature gradually declined almost but not quite to normal. Thereafter it varied between 98.6° and 99.6°. During the febrile period the patient was very carefully studied and nothing was found to account for the fever. He never was very ill. He made no complaint and was mentally clear. The only difficulty which attracted attention was urinary frequency. His urine contained some pus and repeated cultures demonstrated the presence of B. coli. The spleen was not palpable. The Widal reaction was strongly positive. This led to the suspicion that he might have typhoid fever, but there was no confirmation of this view by any of the clinical manifestations nor the bacteriological studies. He was discharged from the hospital on June 21, 1933, greatly improved.

Laboratory Examinations. (First Admission.) Blood Count: April 3, 1933: Hgb. 92%; Red Blood Cells 4,840,000; White Blood Cells 4,400. Smear showed no abnormality. Differential count within limits of normal. May 3: Hgb. 87%; Red Blood Cells 4,470,000; White Blood Cells 4,500. June 10: Hgb. 79%; Red Blood Cells 5,080,000; White Blood Cells 6,100. During the febrile period there usually was a leukopenia, the counts varying from 4,000 to 9,000.

The Wassermann reaction on the blood serum was negative.

Blood culture: April 6: A few diphtheroids on blood agar plates. May 19: No growth. May 26: No growth.

Urine culture: April 20: B. coli. May 1: Heavy growth nonhemolytic Staphylococcus aureus and B. coli. May 20: Staphylococci and B. coli. No organisms of the typhoid dysentery group. May 30: B. proteus. B. coli. No organisms of the typhoid dysentery group. June 2: B. coli. A. streptococci. No organisms of the typhoid dysentery group. June 19: B. coli.

Stool: May 20: No organisms of the typhoid dysentery group. June 5: No organisms of the typhoid dysentery group.

Agglutination tests with blood serum, Widal reaction: May 19: Agglutination with B. typhosus up to dilutions of 1:1280. No agglutination with B. paratyphosus. May 20: No agglutination with B. typhosus or with paratyphosus A and B. May 22: Agglutination with B. typhosus up to dilutions of 1:1280. No

agglutination with B. melitensis. June 2: Agglutination with B. typhosus up to dilutions of 1:640. No agglutination with paratyphosus A and B.

Blood Chemical Studies: April 15: 32 mg. % Non-protein nitrogen. June 5: 30 mg. % Non-protein nitrogen.

Urine: The urine ranged in specific gravity from 1.008 to 1.024. When the patient was first admitted, it contained a considerable amount of albumin as much as half a gram per litre. Later there was only occasionally a trace. Microscopically, a few leukocytes and now and again a small number of hyaline and granular casts.

Phthalein test of kidney function: April 15: Excretion of 50% in two hours.

Stool: Only two examinations are reported and these revealed nothing abnormal. Test for occult blood was negative.

Intracutaneous tuberculin test: Positive in a dilution of 1:1,000. Negative in a dilution of 1:10,000.

The blood pressure varied, systolic from 124 to 160, diastolic 80 to 130. When the patient first entered the hospital the blood pressure was somewhat elevated; subsequently it remained at a lower level, systolic generally between 140 and 150, diastolic between 80 and 90.

The temperature during the first ten days was at the normal level, on a few occasions it went to 99°. On the eleventh day it began to rise and there was fever from April 17 to June 1, varying irregularly from 99° to 103.8°. It then began to decline and thereafter varied between 98.6° and 99.6°.

The pulse on admission was 120. The following day it was 70. From then on it varied between 60 and 80 when the temperature was down, and from 80 to 110 when the temperature was elevated.

Roentgenograms: April 15: Tele: M.R. 4.3, M.L. 7.8, A. 6.6, T. 28. Chest: The heart is normal in size. The aorta dilated. Lungs clear. Bilateral cervical rib. May 24: Chest: Lungs clear. Heart and aorta moderately enlarged. Bilateral cervical rib.

Electrocardiograms: April 4: Normal sinus rhythm. T waves slightly inverted in all leads. April 28: Normal sinus rhythm. Levogram. T III isoelectric.

Course after leaving the hospital. The patient returned to the hospital on July 29, 1933, a little over six weeks after his discharge. He was very dull and mentally somewhat confused so that the account he gave of the course of events during these six weeks was unreliable. During the first three weeks apparently he had gotten on reasonably well; then the digitalis had given out and he had failed to renew it. Soon thereafter he began "to feel just sick, weak and tired all over." On the morning of July 29 he came to the Out-patient Department where it was found that his temperature was 104°. He was immediately admitted to the hospital.

Examination. (Second Admission.) Temperature 103.4°; pulse, 88; respirations, 24; blood pressure, systolic 110, diastolic 68.

The patient was an emaciated old colored man who evidently had lost much weight. He was deeply prostrated and looked to be very ill. He lay flat in bed without dyspnea. He was drowsy, dull and mentally confused. The examination gave the same results as that made on the previous admission except for the following findings: Over the right lower lobe there was dulness and diminished intensity of the breath sounds; a number of sibilant râles were scattered over both lungs, more numerous over the left than over the right; many fine râles were heard over the right lower lobe. The heart is described as having been moderately enlarged to the left: dulness measured 3.2 cm. to the right and 10.5 cm. to the left of the midline; there was a little dulness over the manubrium as before; the heart sounds were clear; there was no gallop rhythm. The abdomen was scaphoid, there was no evidence of fluid; the liver was not definitely felt; the tip of the spleen was felt by some, not by others.

Course in the hospital after second admission. The patient lived but six days after his second admission to the hospital. During that period he lay quietly and contentedly in bed dozing most of the time. There was just a little cough. The temperature was continuously high. He became more and more somnolent and finally died in coma. Signs gradually developed indicating the presence of consolidation in the left lung as well as in the right.

Laboratory Examinations. (Second Admission.) Blood Count: July 29: Hgb. 75%; Red Blood Cells 4,610,000; White Blood Cells 3,160. Throughout the illness there was marked leukopenia, the white count varying from 1,500 to 3,160.

Wassermann reaction on the blood serum was negative.

Blood culture: No growth.

Stool: Showed no organisms of the typhoid dysentery group.

Pharynx: Yielded A. and B. hemolytic streptococci; nonhemolytic staphylococci and diphtheroids.

Sputa: Yielded A. streptococci, nonhemolytic staphylococci and diphtheroids.

Urine: B. coli.

Agglutination test: Widal reaction positive in dilutions up to 1–1280. No agglutination with B. melitensis.

Urine: Contained a trace of albumin and a small number of pus cells.

Stool: Showed no abnormality. Test for occult blood negative.

Spinal fluid: Obtained by cisterna puncture after death showed clear fluid, cells. Pandy negative, Wassermann reaction negative, colloidal mastic test negative.

Roentgenogram: July 31: Chest: Infiltration of both lungs probably due to bronchopneumonia.

The temperature was continuously high, varying from 102° to 106°.

The pulse rate varied from 90 to 120, going 140° shortly before death.

Anatomical Diagnosis: Conglomerate tubercles in aortic lymph nodes. Generalized miliary tuberculosis of lungs, spleen, kidneys, peritoneum. Fibrous adhesions of peritoneum and pleurae.

Malta fever. It is not necessary to add to what has been said about Malta fever in discussing long-continued, low-grade fever. The four cases included in the group of patients having higher fever present in general the same features. As physicians become more thoroughly familiar with the clinical manifestations of this disease, the diagnosis will become proportionately easy.

Tularemia. The case included in our series has already been reported at a clinical pathological conference (5). When an initial lesion and swelling of the regional lymph nodes is present tularemia usually is recognized but the typhoid form is very difficult to diagnose. At first the disease manifests itself as a virulent infection with high fever and deep intoxication. During this stage the physical examination reveals no gross abnormality except that the spleen may be palpable. Later the signs of bronchopneumonia develop. Even at the postmortem examination the correct diagnosis may be missed, since the lesions very closely resemble those of tuberculosis.

Typhoid fever is no longer an important source of difficulty in diagnosis. With the use of the newer bacteriological methods of examination the presence of the typhoid bacillus in blood, urine or feces, rarely escapes detection. We have seen many instances of obscure fever in which typhoid fever was considered a possible cause but the typhoid bacillus could not be cultivated from the blood or excreta. Without exception it finally turned out that all the patients had some other disease. On the other hand, merely the presence of the typhoid or paratyphoid bacillus in the stools does not warrant the diagnosis of typhoid or paratyphoid fever. We recall a middle-aged colored woman who was on the wards for many weeks with obscure fever. Paratyphoid bacilli were grown repeatedly from the stools and this led to a strong suspicion that the patient had paratyphoid fever. Finally the characteristic manifestations of tuberculosis slowly developed. Since anti-typhoid vaccination has become almost universal, a positive Widal reaction has little value in diagnosis. The one case of typhoid fever included in our series was diagnosed purely upon clinical grounds without bacteriological verification and there fore the diagnosis may be questioned. The patient had fever, rose spots, a palpable spleen, a slow pulse and leukopenia. At the end of four weeks the temperature fell to normal and thereafter recovery was prompt and uneventful.

Malaria has become relatively an uncommon disease in Baltimore, but this very fact may increase the possibility of overlooking the occasional case. However, as a matter of routine the blood of every patient entering the hospital is carefully searched for parasites, and when there is unexplained fever, the search is systematically repeated until a satisfactory diagnosis is reached. When patients are under careful supervision in the hospital, the rule is adhered to that quinine shall not be given unless parasites be found. However, when supervision over a long period of time is impossible then quinine may be administered as a therapeutic test. The case included in our series concerns a woman from the counties who had had fever for weeks and came to Baltimore for diagnosis because tuberculosis was suspected. She remained only one day and although tuberculosis was definitely excluded no other cause for the fever was discovered. The blood was carefully examined and no malarial parasites were found. In reply to a letter of inquiry written a month later the patient told that her home physician had given her quinine and at once the fever had disappeared.

Amaebiasis. We are not accustomed to consider infection with Entamoeba histolytica as a cause of obscure fever. Nevertheless, occasionally this relation exists. The past winter an engineer from Chicago entered the Johns Hopkins Hospital complaining of having had unexplained fever for a year and a half. He had been thoroughly and repeatedly studied both at Chicago and Cleveland and no cause for the fever had been found. It may be assumed confidently that his stools had been thoroughly searched for amoebae. In addition to fever and general malaise he complained only of dull discomfort over the region of the liver. On one occasion his physician had heard a friction rub at the base of the right lung. The physical examination was quite negative except for slight tenderness below the right costal margin and a high position of the right diaphragm. The laboratory studies furnished no useful information. Finally Dr. Bauer of the School of Hygiene reported finding a few typical Entamoebeae histolyticae in the stools. The patient was given emetine subcutaneously and after three or four days the temperature fell to normal and thereafter was never again elevated; all the symptoms soon disappeared, and weight and strength returned. Six months

later the patient reported that he had remained perfectly well. Elliot (6) describes a number of similar cases.

4. DISEASES OF THE BLOOD-FORMING ORGANS

Fever often accompanies anemia, (especially pernicious anemia) leukemia, myeloma, lymphosarcoma and Hodgkin's disease. Nearly always the characteristic marks of the disease are present and there is no difficulty in arriving at the correct diagnosis. Aleukemic leukemia occasionally presents a problem, because for a time at least the diagnosis may not be clear. During the past two years we have seen two cases missed clinically in which the correct diagnosis was established at autopsy. One was the case of a colored man admitted to the hospital desperately ill with acute yellow atrophy of the liver of which he died a few days later. In the left groin there was a mass of enlarged lymph nodes and since the blood count was reported to be normal it was assumed that they were due to Hodgkin's disease. Autopsy revealed the characteristic findings of leukemia. The second case was that of an elderly white man admitted to the hospital with high fever and delirium. He died about twenty-four hours later. There was only inconspicuous enlargement of the lymph nodes, and the blood count was recorded as being normal. Here too the postmortem diagnosis was leukemia.

Hodgkin's disease is often accompanied by fever and the fever usually has characteristic features. The temperature is normal for a week or two, then follows a period of fever of approximately equal length, then an afebrile interval, then another bout of fever and so on. As many as thirty or forty successive waves of fever have been observed. The temperature chart closely resembles a record of the undulant fever of melitensis infection and there is the possibility of confusion. As a rule the other symptoms of Hodgkin's disease are clearly defined but occasionally fever may for many months precede any evidence of glandular or splenic enlargement. Recently Jackson (7) has again called attention to this occurrence. We select one of our cases as an illustration.

Case No. 10. J. S. Unit History No. 28281. A white woman, 64 years of age, entered the Johns Hopkins Hospital November 30, 1929, complaining of fever. Her illness had begun a year before with a chill followed by fever lasting two or

three weeks. Then for a while she had been better, but during the course of the year she had had three or four similar periods of fever. It was in the midst of one of these bouts of fever that she entered the hospital.

She was a well-nourished woman seemingly not very ill, although her temperature was 104°. There was a moderate degree of arteriosclerosis of the peripheral and retinal vessels without hypertension (blood pressure, systolic 104, diastolic 70). The tonsils were small and scarred and slightly enlarged lymph nodes were felt at the angles of the jaw. The liver and spleen were easily palpable. The temperature at first was irregularly elevated, usually subnormal in the morning, rising to between 103° and 104° in the afternoon. At the end of two weeks it fell gradually almost to normal but a little later rose again, on this occasion the fever persisting for ten or twelve days. Then followed another period of almost normal temperature, at the end of which high fever again came on and persisted uninterruptedly to the day of death, March 5, 1930. About the middle of December 1929 the enlarged gallbladder was easily felt and a roentgenogram demonstrated that it was filled with stones. On January 20, 1930, the gallbladder was removed. A small nodule was excised from the liver which histological examination proved to be a healed tubercle. The operation had no effect upon the course of the illness. Later dulness appeared over the left lower lobe of the lung with diminished intensity of breath sounds and fine moist râles. The patient gradually lost weight and strength and finally died of exhaustion a little over three months after entering the hospital.

During the period of observation numerous laboratory tests were made which added little information of value. The blood count on admission was hemoglobin 95 per cent., red blood corpuscles 4,440,000, leukocytes 4,500. The differential count was normal. Later the leukocyte count dropped to 2,100 and thereafter remained at a low level. The monocytes of the blood gradually increased in number and at one time made up 18 per cent. of the colorless cells. Repeated blood cultures remained sterile. Agglutination tests for Malta fever and tularemia were negative. The Wassermann test also was negative. Very exhaustive roentgen-ray studies were made of the chest, the abdomen and the bones, but yielded no useful information. The urine at first was normal, at the end of the illness a urinary infection with the colon bacillus came on. Special examinations of the nose and throat, the teeth, the gastro-intestinal tract, the pelvic organs and the urinary tract revealed no significant abnormality.

From these data no satisfactory clinical diagnosis was made. The autopsy revealed Hodgkin's disease of the liver, spleen, abdominal lymph nodes, bone marrow and lungs.

5. MALIGNANT TUMORS

It is well known that malignant tumors often produce fever but the fact is seldom emphasized in diagnosis (8). Modern methods of examination, particularly the development of the roentgen ray, have

made the detection of growths relatively easy, and it is only rarely that they remain undiagnosed for a long time. If one wishes to realize the importance of fever in the diagnosis of malignant disease he must read the medical literature of the closing half of the last century. There it is clearly pointed out that from 40 to 50 per cent of all malignant tumors are accompanied by fever; that fever occurs especially often with tumors of the abdominal organs; that fever is present as often with primary growths as it is when secondary infection or metastasis has occurred. Physicians should be aware that for months unexplained fever may be the sole clinical evidence of the presence of a malignant growth, and whenever obscure fever is met with in an adult, this possibility should always be carefully considered. With our present methods of investigation difficulty in the diagnosis of tumors which cause fever may arise when the growths are unusual in character or, more especially, when they are situated in a location not accessible to our examination. On account of their hidden position tumors of the kidney are particularly difficult to discover and often they may for months give no other evidence of their presence than a continuous fever (9). This is a matter of very great clinical importance and, if remembered, will lead to many shrewd diagnoses. It is noteworthy that of the eight tumors included in our series of cases five were tumors of the kidney. Of particular interest to us were the following cases:

Case No. 11. J. G. Units History No. 27167. A laboratory attendant, twenty-three years of age, entered the hospital complaining of fever and abdominal pain. The leukocyte count was elevated and there was abdominal tenderness especially pronounced in the right lower quadrant. At operation a normal appendix was removed and such investigation as was made revealed no disease of the other abdominal organs. After operation fever continued and gradually the pain and tenderness became localized in the right upper quadrant of the abdomen and finally the liver easily could be felt. The leukocyte count was always high and there was a conspicuous eosinophilia. The patient lost weight and strength. The possibility of Hodgkin's disease was seriously considered, but the opinion of most observers favored the presence of suppuration in or about the liver. At the end of a few months the patient was operated upon a second time and carcinoma of the liver was found. The postmortem examination, performed a little later, disclosed a primary liver-cell carcinoma with widespread metastasis.

Case No. 12. W. P. Unit History No. 23479. A young man, 23 years of age, consulted us complaining of fever and loss of weight and strength which had per-

sisted for about two months. The examination revealed no significant data except enlargement of the spleen. The diagnosis seemed to lie between Hodgkin's disease and tuberculosis. The spleen was removed at operation and microscopical study demonstrated that it was the seat of a malignant endothelioma.

Case No. 13. W. B. G. Dr. C. H. Cocke referred to us for study, a man, 36 years of age, complaining of fever and prostration. A year before he had begun to notice unaccustomed fatigue which gradually had become more and more pronounced. Six months later after a tiring motor trip he had a chill followed by fever. He consulted a number of physicians and all told him his lungs were perfectly clear and that they could find no cause for the symptoms. From then on he continued to have fever and an occasional night sweat, with general malaise and exhaustion. Finally, a diagnosis of tuberculosis was made and the patient went under the care of Dr. Cocke. After a five week period of observation Dr. Cocke came to the conclusion that the illness was not due to tuberculosis and feared that it was carcinoma. Aside from fever, loss of weight and slight anemia the physical examination disclosed only slight signs of pulmonary infiltration at the apex of the right lung, that is, a little dulness and diminished intensity of breath sounds but no râles. The roentgenogram, however, showed a more extensive, sharply defined lesion the nature of which caused much discussion. Some thought it was tuberculous, others a primary tumor, still others a metastatic tumor. From then on the mass in the chest gradually increased in size and the patient lost weight and strength. Treatment with radiation for a time stayed the growth of the mass but later it spread and after an illness of twenty months the patient died. An autopsy was not held but the course of events leaves no doubt that he had pulmonary carcinoma, probably a primary pulmonary carcinoma.

In the introduction to the remarks upon the diagnosis of obscure fever we stated that our interest in the subject had been freshly aroused by an unusually puzzling instance of obscure fever which at last had been correctly diagnosed through a fortunate empirical inference. The facts concerning this patient are so unusual that we deem them of sufficient interest and importance to be reported in detail.

Case No. 14. F. R., Unit History No. 32824. A white woman, 49 years of age, entered the Johns Hopkins Hospital August 28, 1930, complaining of persisting fever. Before the onset of the illness which brought her to the hospital she had always had good health. At eleven years of age she had had a fever lasting for about two months, the nature of which had not been definitely determined. At twenty she had had an attack of pleurisy. About the tenth of May, 1930, she had been at Paris with her husband and daughter, on the point of leaving for London, when all had come down with colds. Upon arriving in London they had consulted a physician who discovered that the patient was running a fever, the temperature

going each afternoon to about 102°. The husband and daughter had promptly recovered from the mild respiratory infection, but although the patient's symptoms had disappeared, she had continued to have fever. She then had entered a nursing home under the care of a prominent London consultant and had spent a month there. During this period she had been very thoroughly examined but no abnormality had been discovered to account for the fever. At the advice of the physician the family had returned home arriving on the fourteenth of June. Then another very thorough and careful investigation had been pursued under the direction of the family physician. Again the examination was astonishingly uninforming. The tonsils were thought to be infected and they had been removed but without the least effect upon the fever. A little later four teeth had been extracted without any apparent benefit. The patient had felt perfectly well and had complained of no symptoms whatsoever except occasionally of a little vague discomfort in the right side of the abdomen. Since no explanation for the fever had been found it was thought probably to be due to an occult tuberculosis. The lungs showed no abnormality except a little fibrosis in the roentgenogram.

Examination. The patient was a well nourished woman who had evidently lost a little weight. She had a good color, was bright and cheerful and did not seem to be at all ill. The eyes were normally prominent; the pupils were equal, regular and reacted actively to light and on accommodation. The extra-ocular movements were well performed. The fundi showed no abnormality. The teeth were in good condition. All of the devitalized teeth had been extracted. The tongue was lightly coated. The pharynx showed nothing remarkable; the tonsils had been completely removed. There was no enlargement of any of the superficial lymph nodes. The thyroid was easily felt, perhaps a little above the average size, of normal consistence. The chest was well formed and symmetrical; movements equal on the two sides. The percussion note over the lungs was everywhere resonant. The breath sounds were normally vesicular. There were no râles The breasts showed no abnormality. The apex beat of the heart was in the fifth interspace inside the nipple line. The area of cardiac dulness was not enlarged. The heart sounds were clear and of normal quality except that the second aortic sound was a little accentuated. The abdomen was normal in appearance. The walls were soft and relaxed, and there were numerous linear striae. There was no tenderness and no masses could be felt. The liver and spleen were not enlarged. There were small Heberden's nodes, otherwise no gross manifestations of arthritis. The deep reflexes were normally active.

Laboratory Examinations. Blood Count: August 27, 1930: Hgb. 80%; Red Blood Cells 5,210,000; White Blood Cells 12,400. Differential: P.M.N., 84%; P.M.E., 0%; P.M.B.; 0%; Mono., 2%; L.L., 5%; S.L., 9%. R.B.C. uniform in size and shape and well filled. No immature forms of R.B.C., or W.B.C. Platelets normal. No parasites. Subsequent leukocyte counts varied from 5,800 to 7,300.

Agglutination Tests: Typhoid bacillus negative. Bacillus melitensis negative.

Cultures: Blood: negative. Stool: negative. Urine: negative.

Blood Chemical Studies: Non-protein nitrogen, 27 mg. %. Uric acid, 3.6 mg. %. Sugar, 125 mg. %.

Wassermann reaction on the blood-serum, negative.

Basal Metabolic Rate: +6%.

Stool: soft, dark brown, semi-formed. No gross blood or mucus. Test for occult blood negative. Micro.: No R.B.C., W.B.C., ova or parasites.

Gastric Analysis: 15 cc. fluid removed, 45 minutes after Ewald Test Meal. Fluid thin, clear with white sediment of food particles; odor normal. Micro.: No R.B.C., W.B.C., or bacteria seen. Acidity: No free HCl. Total acidity 32.5.

Phthalein Test: 1st half hour, 45%; 2nd half hour, 30%; 3rd half hour, 10%; 4th half hour, 5%; total, 90%.

Urine: On admission—negative. Numerous examinations showed an occasional trace of albumin, and fairly regularly a few W.B.C. in the sediment. No definite R.B.C. were seen.

Roentgenograms: August 29, 1930: Chest: Lungs clear. Stomach: No evidence of lesion in stomach or duodenum. Fluoroscopic exam.: Prolapsed orthotonic stomach, functioning normally: no lesion in stomach or duodenum. September 6: Kidneys: Negative for stones. Gallbladder: Gallbladder filled with dye: concentration normal; no gallstones can be seen September 11: Right elbow; hand; right wrist; right knee; right ankle: Slight infectious arthritis of knee; other joints negative.

Special Examinations: Dental Examination: (Dr. Baish) No infection about the teeth. Nose and Throat Examinations: (Dr. Slack) No focus of infection in the nose, throat or ears. Gynecological Consultation: (Dr. Te Linde) Except for a mild chronic cervicitis, the genito-urinary tract is negative. The mild cervicitis can not explain the fever.

At the end of two weeks all of our investigations has yielded only negative results and we were no nearer the solution of the problem than when the patient had entered the hospital. However, during these disappointing weeks a patient who had been observed by us about eight years before recurred to our mind with peculiar insistence. This patient had been the mother of one of the resident surgeons and she had had fever of unknown cause for several months before coming under our care. During the four weeks she had spent in the hospital her temperature each afternoon had risen to between 102° and 103°. In spite of a very thoroughly planned investigation no single abnormality had been discovered to explain the fever. Some months later she had had a hemorrhage from the urinary tract and at operation a large hypernephroma had been discovered. The symptoms of these two patients were so much alike that the conclusion forced itself upon us that both must have the same underlying disease. With only this slender empirical inference to support our rashness we boldly declared that the patient then under observation must have a hypernephroma. Needless to say the statement was received with ridicule for it seemed to be entirely unrelated to any evidence so far unearthed. Nevertheless, we insisted that the patient should not leave the hospital until a careful cystoscopic examination had been made.

FIG. 1. Sept. 17, 1930. Urogram R. side with 17 cc. NaI. Catheter tip at pelviureteral junction. Pelvis about normal, calyx necks slightly dilated. Upper calices apparently displaced toward spine, elongated, and narrowed. Suggestion of denser area laterally. Ureter moderately dilated down to iliac gland region except for a narrow area opposite IV Lumbar vertebra. Left kidney shadow apparently normal. Numerous calcified glands and phleboliths in region of both broad ligaments.

On September 17, 1930, Dr. G. L. Hunner made the cystoscopic examination and pyelograms were taken. The urine from both kidneys was perfectly clear, containing no albumin and no pus cells or red blood corpuscles. The phthalein

output was the same from each kidney. The pyelogram of the left kidney was perfectly normal. On the right the upper calix appeared to be flattened and

FIG. 2. Sept. 24, 1930. Urogram left side, with 10 cc. NaI. Pelvis smaller than normal. Calices slightly dilated. Ureter slightly dilated down to region of broad ligament. Note spleen shadow. Note shadow of upper pole of right kidney opposite 1 Lumbar vertebra and slightly denser shadow outside and below this.

compressed. (Figures 1 and 2.) Dr. Hunner interpreted this as indicating the presence of a tumor in the right kidney which was compressing the upper

calix. Dr. F. H. Baetjer looked at the roentgenograms and thought that the deformity was within the limits of normal and probably did not represent a pathological condition. The opinions of several urologists were sought and views about the situation varied widely. Nevertheless, this was the only single abnormality that had been discovered and it seemed a sufficient warrant for undertaking an

FIG. 3. Photograph of specimen removed at operation. Well defined tumor capsule encroaching on pelvis and upper calices. Tumor mass extending through the upper outer cortex but still well encapsulated by the true and fatty capsules. Careful search at operation failed to reveal enlarged lymph (nodes) in the neighborhood.

exploratory operation. On September 26 the operation was performed by Dr. Hunner. When the right kidney was exposed a tumor mass measuring 5 cm. by 6 cm. in diameter was found in the upper pole. (Figure 3.) The capsule had not been perforated and there was no evidence of metastasis. The patient recovered uneventfully from the operation. The temperature which previously had been elevated each afternoon to between 101° and 102° fell at once, and after a few days

of slight fever came to normal and remained normal thereafter. The patient for a while seemed to be perfectly well and gained in weight and strength. However, the following April fever returned and gradually the indubitable evidence of abdominal metastases developed and from then on the patient's condition grew progressively worse. She died on July 7, 1931.

REFERENCES

(1) Carter, E. P., and Baker, B. M.: Three Instances of Unusual Gonococcal Infection, *Bull. J. H. H.*, **50:** 57, 1932.
(2) Morgan, Hugh: Chronic Meningococcus Septicaemia, *Ibid.*, **32:** 245, 1921.
(3) Thayer, W. S.: Fever in Tertiary Syphilis, *Internat. Clin.*, **4:** 94, 1923.
(4) Futcher, T. B.: Syphilitic Fever, *M. Clin. North America*, **16:** 1067, 1932–1933.
(5) Hamman, L.: Clinical Pathological Conference, *South. Med. J.*, **26:** 665, 1933.
(6) Elliot, C. A.: Importance of the Therapeutic Test for Amebiasis in Patients Presenting Symptoms Referable to the Right Lower Chest, *Tr. A. Am. Physicians*, **50:** 176, 1935.
(7) Jackson, H. J.: Fever As the Main Symptom of Malignant Lymphoma, *M. Clin. North America*, **15:** 4, 983.
(8) Briggs, LeRoy H.: Fever in Carcinoma, *Am. J. M. Sc.*, **166:** 846, 1923.
(9) Creevy, C. D.: Fever in Renal Tumors, *J. A. M. A.*, **92:** 1256, 1929.
Nicholson, Daniel: Fever with Renal Carcinoma, *Arch. Path.*, **3:** 393, 1927.